Enantioselective synthesis of α-fluoro-β-hydroxy esters and amides and Ni-catalyzed asymmetric 1,4-addition to vinylnitriles

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Enantioselective Synthesis of α-Fluoro-β-hydroxy Esters and Amides and Ni-Catalyzed Asymmetric 1,4-Addition to Vinilnitriles

A Dissertation Submitted to the
SWISS FEDERAL INSTITUTE OF TECHNOLOGY ZURICH

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Doctor of Science

Presented by

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Abstract

This thesis is subdivided into two main chapters dealing with the synthesis of fluorinated β-hydroxy esters and amides via asymmetric transfer hydrogenation and the enantioselective 1,4-addition of 1,3-dicarbonyl compounds to vinilnitriles catalyzed by dicationic Ni-complexes, respectively.

A series of chiral and racemic alkyl/aryl α-fluoro-β-keto esters and amides have been prepared via electrophilic fluorination of β-keto esters and amides. The asymmetric transfer hydrogenation of α-fluoro-β-keto esters and amides catalyzed by the [(η⁶-arene)Ru(TsDPEN)] system, originally developed by Noyori leads to the corresponding fluorinated β-hydroxy esters and amides with good yields and enantioselectivities (yields up to 95%, ee up to >99%).

Thus, the four pure enantiomers of fluorinated α-fluoro-β-hydroxy esters and amides can be obtained by this method after chromatographic purification of the corresponding product mixture.

X-ray crystallographic studies of the fluorinated α-fluoro-β-hydroxy ester P3 and amide P10 and their derivatives 17 and 18 have been used for the determination of the absolute configuration of the stereogenic centers generated by asymmetric fluorination and transfer hydrogenation. Moreover, the conformation of those compounds in the solid state is such that a gauche orientation between the C-F and the neighbouring C-O bonds is usually present.
The enantioselective 1,4-addition of 1,3-dicarbonyl compounds to vinylnitriles is catalyzed by dicationic nickel complexes bearing the tridentate chiral ferrocenyl phosphine *Pigiphos*. The products are isolated in good yields and with moderate enantioselectivities (yield up to 99%, ee up to 67%).

Two dicationic \([\text{Ni(Pigiphos)}]^{2+}\) complexes (Ni\(_A\), and Ni\(_B\)) have been prepared and structurally characterized by X-ray crystallographic analysis of the single crystals.
Zusammenfassung

Diese Dissertation enthält zwei Kapitel. Das erste Kapitel behandelt die Synthese von fluorierten β-Hydroxyestern und β-Hydroxyamiden durch asymmetrische Transferhydrierung. Im zweiten Kapitel ist die enantioselektive 1,4-Addition von 1,3-Dicarbonylverbindungen zu Vinylnitrilen, katalysiert durch dikationische Ni-Komplexe beschrieben.


Nach der chromatographischen Reinigung der entsprechenden Produktmischung können auf diese Weise die vier Enantiomerenreinen α-fluorierten β-Hydroxyester oder β-Hydroxyamide erhalten werden.

Die enantioselektive 1,4-Addition von 1,3-Dicarbonylverbindungen zu Vinilnitrilen wird von dicationischen Nickelkomplexen mit tridentaten chiralen Pigiphos-Liganden katalysiert. Die Produkte sind in guten Ausbeuten und mäßigen Enantioselektivitäten isoliert worden (Ausbeuten bis zu 99%, ee bis zu 67%).

Zwei dikationische [Ni(Pigiphos)]^{2+}-Komplexe (Ni_A und Ni_B) wurden hergestellt und durch Röntgestrukturanalyse charakterisiert.
摘要

本论文分为两个部分，它们分别是不对称氢转移反应在合成一系列\( \alpha \)-氯\( \beta \)-羟基酯与酰胺化合物中的应用研究以及镍催化的\( \alpha, \beta \)-不饱和酰胺化合物\( \alpha \)-氯\( \beta \)-酰胺与酰胺底物的不对称\( \alpha \)-氯\( \beta \)-酰胺酯与酰胺化合物。

通过\( \beta \)-酮酸酯和酰胺的亲电氯化反应，我们合成了一系列消旋和手性的\( \alpha \)-氯\( \beta \)-酮酸酯与酰胺化合物。然后，通过应用Noyori的\([\text{Ru} \text{(TsDPEN)}(\eta^5 \text{-arene})]\)体系不对称催化的还原一系列消旋的\( \alpha \)-氯\( \beta \)-酮酸酯与酰胺底物，我们可以高收率和高对应选择性地获得相应的\( \alpha \)-氯\( \beta \)-羟基酯与酰胺化合物。

采用不同构型的\([\text{Ru}]\)配合物作为催化剂，所得混合产物经过柱层析纯化可以得到相应的四个对映体。

为了决定氯化的含氟产物如P3和P10的绝对构型，我们对其相应的衍生物17和18的单晶结构进行了X-射线衍射研究。单晶结构研究表明含氟化合物的C-F键和邻位的C-O键呈gauche式排列。

我们采用\( \text{Ni(II)/Pigiphos} \)催化体系，对\( \alpha, \beta \)-不饱和酰胺化合物的不对称\( \alpha, \beta \)-共轭加成反应进行了研究。该反应给出较高产率，同时反应的ee值最高可达67%。
同时，我们还培养了[Ni(II)(Pigiphos)]络合物的单晶，并对其进行了X-射线衍射研究。
1 Synthesis of α-Fluoro-β-hydroxy Esters and Their Derivatives via Asymmetric Transfer Hydrogenation (ATH)

1.1 Introduction (I) – About the Synthesis of α-Fluoro-β-hydroxy Esters and Their Derivatives

Organic molecules containing fluorine atoms have attracted much attention because they often show different characters as compared to the parent compounds due to the unique properties of the carbon-fluorine bond. Obviously, β-hydroxy or β-amino acids are one of the fundamental units in various natural or unnatural compounds, and their α-fluorinated derivatives are of particular interest.

In general, α-fluoro-β-hydroxy esters or their derivatives are accessible from small fluorinated building blocks by carbon-carbon bond formation, from α-fluoro carbonyl compounds by reduction (different reducing reagents: NaBH₄, “AIH”-reagent, R₃SiH, R₃B, transition-metal-hydride, H₂, and Baker’s yeast, etc.), and from epoxides by ring opening with fluoride equivalents.

1.1.1 Synthesis by C-C Bond Formation of Partially Fluorinated Building Blocks

More than 40 years ago the synthesis of fluorohydrins by condensation of partially fluorinated building blocks with carbonyl compounds was examined. Thereby, the treatment of benzaldehyde, or aliphatic ketones, with bromofluoro acetate under basic condition or the condition of the Reformatsky reaction was found to form α-fluoro-β-hydroxy esters.

1.1.1.1 Classical Aldol-type Reaction

Bergmann reported the first example of classic aldol-type condensation reactions of ethyl fluoroacetate with carbonyl compounds. The use of sodium hydride or sodium ethoxide as base to generate the enolate of the fluorinated ester afforded the corresponding fluorinated β-hydroxy ester although the yield was generally poor (Scheme 1). Moreover, the enolate of α-fluoroketone reacted with formaldehyde to provide the corresponding fluorohydrin (yield, 13.5-16%).
1.1. Synthesis of α-Fluoro-β-hydroxy Compounds

Scheme 1. The first classic aldol reaction of a fluorinated ester.

Over the last two decades such condensation process as have been improved using the lithium enolate of monofluoroacetates.\textsuperscript{3,4} However, the fluorinated esters or amides enolates exhibited poor diastereoselectivity. In the early report by the Welch,\textsuperscript{5a} the lithium enolate of ethyl fluoroacetate was readily prepared and efficiently utilized in the directed aldol reaction giving the corresponding fluorinated hydroxyl ester with some diastereoselectivity (\textit{syn:anti} 1:1 to 1:3.8) (Scheme 2).

\[ \text{F-O-C=O} + \text{RCHO} \xrightarrow{\text{LHMDS, HMPA, THF, -80 °C}} \text{R-O-C=O} \]

\[ \text{R}^1 = \text{CH}_3, \text{Ph, H} \]
\[ \text{R}^2 = \text{(CH}_3)_2\text{C, CH}_3\text{CH}_2, \text{Ph, C}_7\text{H}_8, \text{C}_6\text{H}_5, \text{3,3-dimethyl-2,4-dioxal-1-yl} \]

Scheme 2. Diastereoselective aldol reaction of the lithium enolate of fluoroacetate with ketones or aldehydes.

Subsequently, the directed aldol reaction of the lithium enolate of more bulky α-fluoro ketones with aldehydes was explored by the same group (Scheme 3, \textit{dr} up to 7:1 to 49:1 \textit{syn:anti}).\textsuperscript{5b} It was mentioned that the formation of the major \textit{syn} product was in agreement with the reaction of the \textit{Z}-enolate with ketones.

\[ \text{RCHO} + \text{F-O-C=O} \xrightarrow{\text{LiHMDS, HMPA, THF, -78 °C}} \text{R-O-C=O} \]

\[ \text{R} = \text{Et, Pr, Pr, }^6\text{Bu, C}_6\text{H}_5, \text{3,3-dimethyl-2,4-dioxal-1-yl} \]

Scheme 3. Highly stereoselective aldol reaction of the lithium enolate of i-butyl fluoroacetate with aldehydes.

The first efficient and highly stereoselective preparation of \textit{erythro}-α-fluoro-α-methyl-β-hydroxy alkanethioates was described by the Ishihara (Scheme 4).\textsuperscript{6a} The (\textit{Z})-titanium enolate, generated from the (\textit{Z})-lithium enolate and chlorortriisopropoxypotanium by transmetallation, underwent the aldol reaction with aliphatic as well as aromatic aldehydes in a highly stereoselective manner (\textit{erythro:threo}, 88:12 to 97:3).
Highly diastereoselective reductive coupling of 2-bromo-2,3,3,3-tetrafluoropropanamide (Weinreb amides) with various aldehydes was reported by the Ishihara’s group. The reaction was promoted by the combination of 1.2 eq each of triphenylphosphine and titanium(IV) isopropoxide. Improvement by employing a catalytic amount of titanium(IV) isopropoxide, in the presence of 1.2 eq of triphenylphosphine, afforded the corresponding α-fluoro-α-trifluoromethyl-β-hydroxy amides in high yields with high erythro selectivities, (dr up to 97:3). The aromatic aldehydes displayed high activity and selectivity in the aldol reaction, while reaction with aliphatic aldehydes gave lower yield and selectivity. Aldol condensation of pivaldehyde with the Weinreb amide proceeded in a very inefficient way (only 5% yield).

The authors provided a plausible mechanism as shown in Scheme 6. Amide A coordinated with Ti(OPr)₄ undergoes a bromine abstraction with PPh₃ to generate the titanium enolate B which may have the Z configuration. The enolate reacts with aldehyde via a cyclic chair-like transition state C, leading preferentially to the erythro-isomer of a titanium aldolate D. The aldolate would be subjected to the exchange reaction with phosphonium or phosphorane species formed in situ, providing phosphonium or phosphorane E and the titanium Lewis acid. The former is finally transformed to the product F by quenching, whereas the latter may be recycled to react with A to reenter the catalytic cycle.
Ethyl fluoroacetate is extremely poisonous, causing convulsions, and ventricular fibrillation.\textsuperscript{5a,5c} Alternative to the poisonous ethyl fluoroacetate is a number of prepared silyl enol ethers (Figure 1). They were subjected to aldol reaction with aldehydes or ketones to yield fluorohydrins with fair to good diastereoselectivity.\textsuperscript{8-9} \(\alpha,\alpha\)-Difluoroalkene acetal (Figure 1, I) was prepared by successive treatment of \(\alpha\)-bromo-\(\alpha,\alpha\)-difluoroacetate with activated zinc metal and chlorotrimethylsilane in THF.\textsuperscript{9a} Removal of zinc by filtration afforded a solution of salt-free \(\alpha,\alpha\)-difluoroalkene acetal, which was distilled to give pure acetal I. The bromofluoroketene acetal (Figure 1, II)\textsuperscript{9b} was generated by the same method as for the preparation of I using ethyl dibromofluoroacetate at -20 °C to give isolated pure acetal in 64% yield as a mixture of isomers (E/Z 62:38), determined by \(^{19}\text{F}\) NMR and confirmed by the NOE between the fluorine and the methyl proton of the ethoxy group. Less attention has been paid to the synthesis and synthetic application of the monofluoroacetal (Figure 1, III). Recently, Chen and co-workers reported the stereoselective synthesis of (E)-ethyl \(\alpha\)-fluoro silyl enol ether by the reaction of ethyl chlorofluoroacetate with activated zinc and chlorotrimethylsilane in DMF or HMPT in high isolated yield (82%).\textsuperscript{8a} And the configuration of acetal III was specified by \(^{1}\text{H}\)-NOESY.

Figure 1. Various fluoroketene acetals.
This (E)-ketene acetal III, in the presence of trimethylsilyl triflate in methylene chloride, reacted with electron deficient aromatic aldehydes to give 1:1 mixtures of the corresponding diastereomeric fluorohydrins in high yield. Electron-rich aromatic and aliphatic aldehydes are inert to the reaction with the ketene acetal. However, the reaction could be promoted by CuCl in HMPA. Under these conditions, also electron-rich aromatic aldehydes, aliphatic aldehydes, such as butyraldehyde or crotonaldehyde and even ketones, such as cyclohexanone or acetophenone, gave mixtures of the diastereomeric fluorohydrins in high yields (Scheme 7).  

\[
\begin{align*}
\text{Scheme 7. Aldol reaction of fluoroalkene acetal with ketones or aldehydes promoted by copper(I)}
\end{align*}
\]

The synthesis of the enantioenriched \(\alpha\)-fluoro-\(\beta\)-hydroxy esters or their derivatives via aldol-type reaction has not drawn much attention. In 1989 Kitazuma reported the Lewis-acid-catalyzed aldol reaction between enol silyl ethers or silyl ketene acetics and the optically active \(\alpha\)-fluoroaldehyde, prepared from (S)-ethyl 2-fluoro-2-methylmalonate by asymmetric enzymatic hydrolysis (Scheme 8).  

\[
\begin{align*}
\text{Scheme 8. Stereoselective aldol reaction of fluorinated ketone and enol silyl ethers promoted by different Lewis acid.}
\end{align*}
\]
1.1. Synthesis of α-Fluoro-β-hydroxy Compounds

The first Lewis-acid-catalyzed asymmetric Mukaiyama’s aldol reaction for the preparation of optically active α-fluoro-β-hydroxy esters was reported by the Iseki group. The salt-free α,α-difluoroketene silyl acetal, prepared in pure form, reacted with various aromatic or aliphatic aldehydes in the presence of catalytic amount of Lewis acid 1 or 2 to afford optically active α,α-difluoro-β-hydroxy esters in good to excellent yield (Scheme 9, >99% yield, up to 98% ee).

![Scheme 9](image)

Scheme 9. Catalytic asymmetric aldol reaction of aldehydes with α,α-difluoroketene silyl acetal promoted by Lewis acids.

The same group extended the scope of silyl enol ether to bromofluoroketene acetal. The enantioselective aldol reaction of bromofluoroketene acetal (Figure 1, type II, 1.2 eq) reacted with various aldehydes in the presence of a catalytic amount of a chiral Lewis acid at -78 °C, affording the corresponding syn- and anti-α-bromo-α-fluoro-β-hydroxy ester with high enantioselectivities (up to 99% ee). The reaction temperature has a great influence on the stereoselectivity. At -20 °C, the aldol reaction proceeds with high enantio- and diastereoselectivities to preferentially afford the anti-aldols having opposite signs of optical rotation as compared to those obtained at -78 °C (Scheme 10).

![Scheme 10](image)

Scheme 10. Oxazaborolidone-catalyzed aldol reaction of bromofluoroalkene acetal with aldehydes

The enantioselective synthesis of anti-α-fluoro-β-hydroxy ketones catalyzed by an amino alcohol was recently reported by Barbas III. The products were obtained with good regio-,
1.1. Introduction

diastereo- and enantioselectivities (Table 1, anti: syn 3:1 to 10:1, regioselectivity: 1:4 to >20:1, ee up to 87%) in moderate to good yields (up to 82%). The absolute configurations of anti-a-fluoroaldols were assigned to S based on the X-ray crystal structure of a fluoroalcohol (entry 1, R = p-nitrophenyl) and by conversion of a fluoroalcohol (entry 2, R = phenyl) to a known product.

The observed enantioselectivities of the reactions can be rationalized by invoking an enamine mechanism operating through a chair transition state where the si-face of an E-enamine of fluoroacetone and L-prolinol attacks the re-face of the aldehyde to provide the anti-a-fluoroalcohol product (Figure 2).

Table 1. anti-a-Fluoroaldols prepared from prolinol-catalyzed aldol reaction of aldehydes and fluoroacetone

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt; (<a href="">anti:syn</a>)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Regioselectivity (A/B)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;d&lt;/sup&gt; (&lt;anti&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-NO&lt;sub&gt;2&lt;/sub&gt;-phenyl</td>
<td>7:3</td>
<td>82</td>
<td>47:3</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Phenyl</td>
<td>9:1</td>
<td>72</td>
<td>&gt;20:1</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>9:1</td>
<td>51</td>
<td>1:4</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>10:1</td>
<td>50</td>
<td>&gt;20:1</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>Cyclohexyl</td>
<td>5:1</td>
<td>34</td>
<td>&gt;20:1</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>iso-butyl</td>
<td>3:1</td>
<td>29</td>
<td>&gt;20:1</td>
<td>79</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by 1H NMR spectroscopy.  <sup>b</sup> Overall yield.  <sup>c</sup> The ratio (A/B) is that of the diastereomers/regioisomer.  <sup>d</sup>The ee of the anti-isomer was determined by chiral HPLC.

Figure 2. A proposed chair transition state in aldol reaction
1.1. Synthesis of α-Fluoro-β-hydroxy Compounds

It should be mentioned that the catalytic asymmetric nitroaldol (Henry) reaction of 2,2-difluoroaldehydes with nitromethane in the presence of lanthanoid-lithium-BINOL complexes (LLB catalyst) provided the corresponding (S)-nitroaldol with moderate to high enantioselectivities in good yields (Scheme 11). The absolute configuration of the fluorinated nitroaldols are reversed with respect to that of the nonfluorinated nitroaldols, which implies that the fluorine atoms in the α-position play an important role in the enantiofacial selection.

![Scheme 11. Asymmetric nitroaldol reaction of 2,2-difluoroaldehydes and nitromethane.](image)

### 1.1.1.2 The Reformatsky Reaction

The first Reformatsky reaction (Scheme 12) of ethyl bromofluoroacetate with aldehydes for the preparation of α-fluoro-β-hydroxy esters was reported by McBee in 1955. The application of the Reformatsky reaction to 2,2-difluoro-3-hydroxyester was described by Hallinan and Fried.

![Scheme 12. Common Reformatsky reaction](image)

Subsequently, improvements of the Reformatsky reaction have appeared in recent reports. One of these involved the use of ethyl chlorofluoroacetate with magnesium activated by iodine in benzene to react with carbonyl compounds. Recently Shen and Qi reported that the Reformatsky reaction of ethyl chlorofluoroacetate with aldehydes in the presence of a catalytic amount of lanthanide complex using DME as the solvent provided high isolated yield. The methods were improved applying ethyl bromofluoroacetate and zinc in the presence of iodine in a mixture of diethyl ether and THF or with zinc in boiling THF. Dolbier and co-workers reported that the Reformatsky reactions of ethyl
bromofluoroacetate with aldehydes and ketones in the presence of catalytic amounts of 
CeCl₃·7H₂O afforded α-fluoro-β-hydroxy esters in highly isolated yields (60-95%). Some 
diastereomers of the fluorinated esters were easily separated by conventional chromatography 
and mild alkaline hydrolysis with a cold 0.2 M ethanolic solutions of sodium hydroxide gave 
α-fluoro-β-hydroxy acids in excellent yields (88-96%). Very recently, Kumadaki reported that 
the Reformatsky reaction of ethyl bromodifluoroacetate with a variety of carbonyl compounds 
in the presence of RhCl(PPh₃)₃ in CH₃CN afforded α,α-difluoro-β-hydroxy ester in high 
yields (72-94%).

The diastereoselective Reformatsky reaction of ethyl dibromofluoroacetate with 
equimolar amounts of aliphatic or aromatic aldehydes afforded a mixture of diastereomeric 2-
bromo-2-fluoro-3-hydroxy esters (erythro:threo 3:2) in the presence of equimolar amounts of 
zinc and diethylaluminum chloride in 65-75% yields (Scheme 13). Employing excess 
aldehyde (2.1 eq) in the presence of zinc (2.1 eq) and diethylaluminum chloride (2.1 eq) 
afforded the corresponding adduct as a mixture of two diastereoisomers (dl:meso = 56/44 to 
66/34) in high yields (70-80%).

The diastereoselective Reformatsky reaction of ethyl dibromofluoroacetate with aldehyde 

The first enantioselective Reformatsky reaction of α,α-fluoroacetate with aldehydes in the 
presence of carbinols, amino alcohols, or amino alkoxides was published by Braun (Scheme 
14). The highest enantioselectivity of the adduct 4 was obtained using N-methylephedrine 3c 
(2 eq) as chiral additive and excess methyl bromodifluoroacetate (3 eq) (84% ee, after 

Scheme 13. The diastereoselective Reformatsky reaction of α,α-dibromo-α-fluoroester with 
aldehyde

Scheme 14. The first enantioselective Reformatsky reaction of methyl bromodifluoroacetate 
and aldehydes.

The highest enantioselectivity of the adduct 4 was obtained using N-methylephedrine 3c 
(2 eq) as chiral additive and excess methyl bromodifluoroacetate (3 eq) (84% ee, after
recrystallization >96% ee). And the absolute configuration of the product 4 was determined by an X-ray structural analysis of the corresponding amine 5.

Another group also described the synthesis of chiral α,α-fluoro-β-hydroxy esters by enantioselective Reformatsky reaction of ethyl bromo-α,α-difluoroacetate 2 with various aldehydes in the presence of chiral amino alcohols with good enantioselectivity (Scheme 15, 38-69% yields, 41-83% ee). The best result was obtained for a molar ratio of aldehyde/Reformatsky reagent/amino alcohol 3b=1:4:1 (69% yield, 83% ee).

Very recently, Knöchel described an improved asymmetric Reformatsky reaction mediated by (-)-N,N-dimethylaminoisoborneol (Scheme 15). Diethyl zinc (0.7 eq) was used for the deprotonation of the amino alcohol in order to avoid using an excess of the Reformatsky reagent. The highly enantioselective formation of α,α-difluoro-β-hydroxy esters was achieved by using 1.1 eq of the Reformatsky reagent in the presence of 1.2 eq of (-)-DAIB and 0.7 eq of diethylzinc (ee up to 90%).

1.1.2 Synthesis by Reduction of α-Fluorocarbonyl Compounds

Since asymmetric electrophilic fluorination of β-keto esters or other β-carbonyl compounds has been well developed to provide α-fluoro-β-keto esters or their derivatives in high yields and with excellent selectivity, the direct reduction of those fluorinated carbonyl
compounds to give α-fluoro-β-hydroxy compounds is demanding and essential. The hydrogen source is mainly based on the traditional metal-hydride reagents (NaBH₄, A1H reagents), some organic hydride reagents (R₃SiH, R₃B), H₂ (hydrogenation), 2-propanol or Et₃N/HCOOH (transfer hydrogenation), and Baker’s yeast, etc.

1.1.2.1 Reduction of Fluorinated Carbonyl Compounds by Traditional Reducing Agents

Enantiopure (S)-(−)-2-fluoro-2-methyl malonic acid monoethyl ester was selectively reduced with N,N-dimethyl-chloromethyleneiminium chloride and sodium borohydride to give good yield of optically pure (S)-(−)-ethyl 2-fluoro-3-hydroxy-2-methyl propionate (Scheme 17).

\[
\begin{align*}
  \text{EtO}_2\text{C} & \text{CO}_2\text{H} \\
  \text{Me}_2\text{F} \quad \text{1. COCl}_2, \text{DMF}, \text{CH}_2\text{Cl}_2 \quad \text{EtO}_2\text{C} \text{CO}_2\text{H} \\
  \text{Me}_2\text{F} \quad \text{2. NaBH}_4, \text{MeCN}, \text{THF} \quad \text{EtO}_2\text{C} \text{OH}
\end{align*}
\]

Scheme 17. Reduction of chiral fluorinated ester by NaBH₄

The trisubstituted silanes reduced the optically enriched α-fluoro-α-methyl-β-keto esters to α-fluoro-α-methyl-β-hydroxy esters with high diastereoselection. Four diastereomeric products were obtained via different reducing systems (Scheme 18). In the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF) in N,N-dimethylformamide (DMF), enantiomerically pure (R)- or (S')-α-fluoro-α-methyl-β-keto esters were reduced by triphenylsilane to the diastereomeric products (anti:syn 21:79 to 4:96). The selectivity in the TBAF-catalyzed reduction was explained by the Felkin models. On the other hand, the diastereocontrolled transformation of α-fluoro-α-methyl-β-keto esters with triphenylsilane-AlCl₃ in dichloromethane afforded the highly diastereomERICally enriched products (anti:syn 97:3 to 99:1). The AlCl₃-catalyzed reduction was interpreted by the chelation model. Moreover, the method was applied to reduce the enantiomerically enriched α-fluoro-α-methyl-β-keto ester by Sodeoka to give highly diastereomERICally pure product (dr = >95:5, in 83% yield).
A catalytic enantioselective reduction of an α-fluoroketone with an (R)-oxazaborolidine catalyst (20 mol%) and catecholborane in toluene afforded the corresponding fluorohydrin with 92% ee in good yield (Scheme 19).\textsuperscript{18a} The method was efficiently applied in the total synthesis of useful molecules.

The classical borane reducing agent (R)-Alpine-Borane® was also used for the reduction of α-fluoroacetophenone to give the (R)-configured fluorohydrin with 89% ee. Aliphatic fluoroketones were reduced with lower enantioselectivity (65% ee) (Scheme 20).\textsuperscript{18b}
1.1.2.2 Asymmetric Hydrogenation

The first ruthenium-promoted hydrogenation reaction of fluorinated β-keto esters has been reported by Noyori and his coworkers on ethyl 4,4,4-trifluoro-3-oxobutanoate using RuHCl-[(R)-BINAP]$_2$ at 80 bar pressure and 30 °C. The corresponding β-hydroxyester was isolated in 95% yield with 46% > ee.\textsuperscript{19a} Genet reported the asymmetric hydrogenation of fluorinated β-keto esters using the in situ generated chiral ruthenium catalysts (Scheme 21).\textsuperscript{19b} The corresponding β-hydroxy esters were obtained in quantitative yield with moderate to good ee (42-95% ee).

Scheme 21. Asymmetric hydrogenation of fluorinated β-ketoesters

Table 2. Enantioselective hydrogenation of various β-keto esters catalyzed by chiral rhodium complexes.

<table>
<thead>
<tr>
<th>entry</th>
<th>R of β-keto esters</th>
<th>temp. (°C)</th>
<th>yield (%)\textsuperscript{a}</th>
<th>ee (%)\textsuperscript{b} (config.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$</td>
<td>30</td>
<td>93</td>
<td>96 (R)$^c$</td>
</tr>
<tr>
<td>2</td>
<td>(CH$_3$)$_2$CHCH$_2$</td>
<td>70</td>
<td>95</td>
<td>92 (R)$^c$</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>30</td>
<td>97</td>
<td>84 (R)$^d$</td>
</tr>
<tr>
<td>4</td>
<td>PhCH$_2$</td>
<td>30</td>
<td>63</td>
<td>94 (R)$^c$</td>
</tr>
<tr>
<td>5</td>
<td>PHCH$_2$CH$_2$</td>
<td>30</td>
<td>100</td>
<td>96 (R)$^c$</td>
</tr>
<tr>
<td>6</td>
<td>PhCH$_2$OCH$_2$</td>
<td>30</td>
<td>95</td>
<td>95 (R)$^d$</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield. \textsuperscript{b} Determined by HPLC. \textsuperscript{c} The absolute configuration was assigned using the modified Mosher method. \textsuperscript{d} The β-hydroxy ester was shown to have the (R)-configuration by conversion to the known corresponding methyl ester.
1.1. Synthesis of α-Fluoro-β-hydroxy Compounds

The highly enantioselective synthesis of 2,2-difluoro-3-hydroxycarboxylates has been recently achieved by hydrogenation of 2,2-fluoro-3-oxocarboxylate in the presence of chiral rhodium-(amidephosphine-phosphinite) complexes generated \textit{in situ} by the reaction of [Rh(COD)OCOCF_3]_2 and the chiral ligand (Table 2.).

The first example of heterogenous enantioselective hydrogenation of an α-fluoro-β-keto ester was reported by Szöllosi (Scheme 22). The optimal reaction conditions were catalytic amount of Pt/Al_2O_3 (5 mol%) and O-methylcinchonidine (2 mol%), in the solvent mixture 1/1 AcOH/THF, under 0.1 MPa H_2 pressure, at 273 K. Under these conditions, dynamic kinetic resolution (DKR) of racemic ethyl 2-fluoroacetate took place to afford the α-fluoro-β-hydroxy ester with high diastereo- and enantioselection (82% ee threo/erythro 99:1). It was pointed out that the racemization of the unreacted starting material was possible because that the reaction rate of the S-enantiomer of the α-fluoro-β-keto ester is 20 times larger than that of the R-enantiomer, and the fast equilibration of the keto (1) and enol forms (3) continuously shifts the reaction in the favored direction, i.e., the generation of chiral alcohol with S-configuration. The enol species could be stabilized by an intramolecular hydrogen bond, similarly as described for 4,4,4-trifluoroacetoacetate.

\[ \text{Scheme 22. Highly selective heterogeneous hydrogenation of a fluoro keto ester via DKR.} \]

1.1.2.3 Asymmetric Transfer Hydrogenation (ATH)

Application of ATH in the asymmetric reduction of halogenated carbonyl compounds was reported by several groups. Most of the investigation focused on the transfer hydrogenation of α-chlorinated ketones. This topic will be discussed in detail in the introduction II (see chapter 1.2, ATH of ketone).

Very recently, Lassaletta has reported the enantioselective synthesis of α-haloalcohols via dynamic kinetic resolution (DKR) upon asymmetric transfer hydrogenation of a variety of cyclic α-halo ketones using the Noyori/Ikariya catalyst and either HCOOH/NEt_3 or HCOONa/“Bu_4NBr in H_2O/CH_2Cl_2 as the hydrogen source (Scheme 23). This is also the first example to obtain optically active fluorohydrin via asymmetric transfer hydrogenation.
Fluorohydrins were obtained with high selectivity (97:3 cis/trans, 97% ee) in excellent yield (98%) under the optimal condition (1.2:1 HCO₂H/Et₃N, 0.5 M initial concentration of fluoroketone).

Scheme 23, Transfer hydrogenation of α-haloketones via DKR catalyzed by the Noyori-Ikariya’s complex.

1.1.2.4 Enzymatic Reduction Reaction

It is well known that baker’s yeast reduction of carbonyl compounds is cheap and easily handled. Stereoselective reduction of optically active α-fluoro-α-methyl-β-keto esters by active fermenting baker’s yeast provided the highly diastereomerically pure α-fluoro-α-methyl-β-hydroxy esters (Scheme 24). (S)-α-Fluoro-α-methyl-β-keto esters were transformed to give erythro-β-hydroxy esters with >99% selectivity, while R-enantiomers were reduced to give threo-β-hydroxy esters with >98% selectivity.

Scheme 24. Yeast reduction of α-fluoro-β-ketoester

1.1.3 Nucleophilic Fluorination of Epoxide

Ring opening of epoxides with hydrofluorinating reagents is a useful method for the synthesis of fluorohydrins. There are some nice reviews on the field. The products of the ring opening of epoxides are 1-fluoro-2-hydroxy compounds (fluorohydrins), which are slightly functionally different from the α-fluoro-β-hydroxyesters. The first asymmetric ring
opening of epoxides was reported by Haufe. Heating of cyclohexene oxide with KHF$_2$/18-crown-6 in the presence of 100 mol% of (S,S)-(+-)(salen)CrCl complex in DMF at 60 °C gave a 89:11 mixture of (R,R)-(++)-2-fluorocyclohexanol (55% ee) and the corresponding chlorohydrin (20% ee) (Scheme 25).\(^{27}\)

\[
\begin{align*}
\text{KHF}_2/18\text{-crown-6, (salen)CrCl} & \quad \text{DMF, 60 °C, 80 h, 92% conv.} \\
+ & \\
\text{(salen)CrCl} & \\
\end{align*}
\]

\[
\text{89 (55% ee) : 11 (20% ee)}
\]

Scheme 25. Ring opening of epoxides with KHF$_2$ promoted by a Cr-salen complex.

In the presence of (salen)CrCl complex and 150 mol% of AgF in a strongly coordinating solvent, reaction of several meso-epoxides provided the corresponding fluorohydrins without any contamination with chlorohydrins with moderate enantiomeric excess (Scheme 26).\(^{28}\)

Some other ring opening of epoxides was investigated and the mechanism was discussed as a competing $S_N1/S_N2$-type process.

\[
\begin{align*}
\text{mol% (salen)CrCl} & \quad \text{temp, yield%, ee%} \\
n = 1, & \quad 100 \text{ mol%}, \ 50 \ ^\circ \text{C}, \ 80, \ 62 \\
n = 2, & \quad 100 \text{ mol%}, \ 50 \ ^\circ \text{C}, \ 90, \ 72 \\
n = 3, & \quad 50 \text{ mol%}, \ 60 \ ^\circ \text{C}, \ 82, \ 65 \\
\end{align*}
\]

Scheme 26. (Salen)CrCl-catalyzed ring opening of epoxide by AgF.

In summary, a variety of methods for regio- and stereoselective preparation of $\alpha$-fluoro-$\beta$-hydroxy esters and their derivatives are known. Asymmetric C-C bond formations via aldol and the Refomatsky reaction involving fluorinated building blocks and enantioselective reduction of $\alpha$-fluoro carbonyl compounds were shown to be practical and useful.
1.2 Introduction (II) - for Asymmetric Transfer Hydrogenation (ATH) – Development and Application of Noyori-Ikariya’s Complex

One of the most fundamental transformations in synthetic chemistry is the asymmetric reduction of the C=O and C=N bonds to form stereogenic centers. Asymmetric transfer hydrogenation (ATH) is an attractive method in view of its operational simplicity and high selectivity.

Transition-metal-catalyzed asymmetric transfer hydrogenation has become an attractive alternative to reduction using gaseous hydrogen. The first example of a transition-metal-catalyzed transfer hydrogenation was reported in the 1960s. A iridium hydride DMSO complex was employed as the catalyst. Ruthenium complexes have more recently been found to be excellent catalysts in hydrogen transfer reactions. After the first ruthenium-catalyzed transfer hydrogenation of practical use was reported by Sasson and Blum, many research groups have further developed ruthenium-catalyzed transfer hydrogenation, such as Bäckvall, Shvo, Yi, Casey, and Noyori and others (Figure 3).

The field is covered by numerous publications including nice reviews discussing mechanism, ligands, solvents, substrates etc. Herein, we concentrate on discussing the development and application of Noyori-Ikariya’s catalyst in transfer hydrogenation. Additionally, the very recent application of the catalyst in other enantioselective reaction such as asymmetric hydrogenation and Michael addition is briefly reviewed.

1.2.1 Hydrogen Donors and Promoters

Isopropanol (iPrOH, IPA) and formic acid/triethylamine (NEt₃/HCOOH, TEAF) are by far the mostly used sources of hydrogen in transfer hydrogenation. IPA is most frequently used also as the solvent of the reaction. The life-time of many metal catalysts in IPA solution is usually reasonably long even at reflux temperature, which allows for most reactions to be
driven to high conversion. However, isopropanol is involved in a ketone:alcohol equilibrium deteriorating the enantioselectivity and preventing a complete conversion. This limitation can be overcome by continuously distilling off acetone as soon as it is formed or by operating the reaction in dilute solution.

Formic acid and its salts are better suited H-donor than IPA because their dehydrogenation in an open system is substantially irreversible due to the evolution of CO₂. An azeotropic 5:2 mixture of HCOOH and NEt₃ (TEAF, a single phase at room temperature) is most frequently employed as reducing agent. It allows for high substrate concentrations and brings about high conversion without back-reaction and racemization. There are some restrictions to the use of TEAF. Several complexes undergo fast decomposition on attempted dissolution in formic acid, and some others lose completely their catalytic activities, probably because the acid inhibits one of the activation process promoted by the base.

Noyori-Ikariya’s catalyst works well in both solvents systems described above. ATH of ketones by Ru-TsDPEN in isopropanol affords high yield and selectivity, while ATH of imines proceeds well in the formic acid-triethylamine azeotropic mixture.

In order to improve catalyst reactivity, selectivity and turn over frequency of the reaction, co-solvents were investigated. Noyori revealed that a 5:2 formic acid-triethylamine azeotropic mixture in acetonitrile containing Ru-(R,R)-TsDPEN is the best system for ATH of imines (>99% yield, up to 96% ee). The reaction was conducted equally well in various aprotic polar solvents including DMF, DMSO, and CH₂Cl₂, but not in ethereal or alcoholic media. The reaction in neat formic acid-triethylamine was very slow. Recently, asymmetric transfer hydrogenation of 1-aryl-2-imidazol-1-yl-ethanone was surveyed using [(R,R)-TsDPEN]Ru(cymene)Cl as precatalyst with 10 eq of a mixture of formic acid-triethylamine (1:1) in different solvents. Acetonitrile gave the highest reactivity but moderate selectivity. Dichloromethane emerged as the pre-eminent solvent giving one of the best selectivities and nearly complete conversion at S/C = 1000. In isopropanol, MTBE, or toluene similar selectivities as in CH₂Cl₂ are obtained. However, the reaction slowed down considerably (Scheme 27).

Scheme 27. Effect of solvent on reaction selectivity and rate
Xiao and co workers realized ATH of various simple aromatic ketone using Ru-TsDPEN catalyst without any modification of the Ru-catalyst in aqueous HCOONa. The reaction system containing water furnished slightly decrease enantioselectivity, but significantly higher rates than in the HCOOH-NEt₃ azeotrope, showing that water can be beneficial for a catalytic reaction in terms of activity, selectivity and productivity. Another report shows that ATH of ketones, especially α-bromomethyl aromatic ketones, catalyzed by unmodified transition metal-amido complex (TsDPEN-M, M= Ru, Rh, Ir), was performed with significant enhancement of activity, chemoselectivity, and enantioselectivity (up to 99% ee) in aqueous mediate containing micelles and vesicles.

Recently, imidazolium ionic liquids (ILs), a new class of reaction solvents, were used as a medium in combination with a formic acid-triethylamine azeotropic mixture in ATH of acetophenone derivatives. Noyori’s catalyst was recycled and reused five times to give product with comparable selectivity in high conversion.

1.2.2 Development and Modification of Ligands

The ligands used in asymmetric transfer hydrogenation include various donor atoms such as nitrogen, oxygen, phosphorus, and sulfur. They can be bidentate, tridentate and tetradentate (Figure 4). The most effective ligands are 1,2-amino alcohols and monotosylated diamines while complex with 1,2-amino alcohols are considerably unstable in formic acid-triethylamine.

Noyori’s complex containing a monotosylated diamine ligand is the catalyst with the broadest scope as it provides significant ee’s with a large variety of substrates. Noyori-Ikariya’s catalyst was prepared by treatment a monotosylated diamine with [RuCl₂(η⁶-mesitylene)]₂ under basic condition. The catalyst precursor and the reactive intermediate were synthesized and characterized by X-ray crystallographic analysis.

Figure 4. Amino alcohol and diamine ligands for asymmetric transfer hydrogenation.
The auxiliaries of the Ru catalysts have a crucial influence on the rate and enantioselectivity of the reaction, which was studied carefully by Noyori and other groups. The RSO₂ functionality in the DPEN series is crucial for the reduction affecting the nucleophilicity of the neighbouring nitrogen and of the NH₂ in the Ru complex. The reactivity of the Ru-catalyst tends to decrease with increasing electron-withdrawing ability of the nitrogen substituents, namely, in the order of C₆H₅CO > p-CH₂OC₆H₄SO₂ > C₆H₅SO₂ > CF₃SO₂, while the sulfonylated compounds give a higher enantioselectivity. Recently, Mohar demonstrated that enhanced enantioselectivity was reached by switching the tosyl group of TsDPEN with other arenesulfonyl groups and, in general, hindered ligands performed better. On the contrary, Mioskowski and co-workers revealed that the activity and stereoselectivity of the catalyst are improved by introducing electron-withdrawing fluorosulfonyl groups on the TsDPEN ligands. ATH of a β-keto α-amino acid via DKR showed that the pKₐ value of the ligand influences the activity and enantioselectivity: the activity of the catalyst is improved by a decrease of the pKₐ of the sulfonamide group and by a decrease of the basicity of the NH₂.

The presence of the NH₂ terminus in the TsDPEN auxiliary is crucially important. The NHCH₃ analogue showed a comparable enantioselectivity but with much lower reactivity; the N(CH₃)₂ derivative gave very poor reactivity and stereoselectivity. Recently, Wills provided a proof that the configuration of the alcohol follows from the stereochemistry of the carbon bound to the tosylamine. And the matched combination of the two stereogenic centers is required for a high stereoselectivity. The trans orientation of the substituents attached to the two stereocenters provides both an improved stereocontrol and a higher reaction rate.

The reactivity of the catalyst decreases in the order of benzene > p-cymene and mesitylene > hexamethylbenzene as a ligand coordinated to Ru, while mesitylene or p-cymene display a better enantioselection than unsubstituted benzene. The η⁶-arene fragment contributes significantly to the performance of these catalyst because of a C(sp³)H/π interaction stabilizing the transition state. And the polyalkylated arenes generally provide higher ee’s because a stabilization of the transition state is improved due to the increased π-donation of the arene and/or due to the contribution of an attractive secondary C(sp³)H/π interaction (Figure 6).
1.2. Asymmetric Transfer Hydrogenation

Figure 6. The CH/π interaction in the transition state (Ru-monohydride mediates H-transfer via metal-ligand bifunctional catalysis (outer sphere mechanism)).

The Noyori-Ikariya’s catalyst has been modified in various ways. Wills developed a new class of “tethered”-catalyst based on the Noyori-Ikariya’s catalyst (Figure 7). The complexes contain a tether between the arene or cyclopentadienyl and TsDPEN components. The tethered catalysts are shown to bring significant activity and enantioselectivity, probably because the tether introduces a further element of stereochemical rigidity of the catalyst.

Figure 7. Tethered catalysts

By solving the problem of the separation and recycling of the expensive or toxic catalysts, an application of the efficient catalyst in industry can be possible. An improvement is to synthesize water soluble ligands by attachment of sulfonated group to the phenyl group, and their metal complexes can be used in aqueous media, which brings the simple product separation and the possibility of catalyst recycling (Figure 8).

Figure 8. Water-soluble ligands

Recently, various modified monotosylated diamine ligands were synthesized, and the corresponding metal (Ru, Rh, Ir)-complexes are active and recyclable. Polymer-supported ruthenium precatalysts, prepared by Wang and Xiao respectively, are highly effective and recyclable for heterogeneous ATH of aromatic ketones. Tu immobilized chiral Ru-TsDPEN
onto amorphous silica gel to obtain a highly practical, efficient heterogeneous Ru-catalyst for ATH of various aromatic ketones in HCOONa-H2O. The catalytic system can be recovered and reused in multiple consecutive catalytic runs (up to 10 uses without recharging of Ru) with maintained high enantioselectivity.52 Dendritic ruthenium complexes with TsDPEN were developed and applied in ATH of ketones, ketoesters, enones, imines, and activated olefins in formic acid-triethylamine azeotrope with good to excellent enantioselectivities comparable to those of the monomeric catalyst.53 The modification of Noyori’s catalyst by attaching imidazolium fragment to the arene coordinated to ruthenium or to the tosyl group was reported by Dyson and Ohta, respectively. The highly recyclable and reactive Ru-complexes were used in ATH of ketones in a mixture of formic acid and triethylamine azeotrope containing ionic liquid affording chiral alcohol with excellent ee’s in high yield through all the catalytic cycles (up to 5 times recycling).

1.2.3 Mechanism

Hydrogen transfer reactions proceed through different pathways. For the Meerwein-Ponndorf-Verley (MPV) reduction, “direct hydrogen transfer” via a six-membered transition state was proposed,54 which is mostly suitable to the non-transition metal-catalyzed reduction reaction. An exception is to explain the mechanism of the reduction with a Ru-complex via the direct hydrogen transfer as proposed by Park.55 For transition-metal-catalyzed transfer hydrogenation, hydridic routes are usually provided, which will be discussed in detail, and Noyori’s catalyst follows this mechanism. Additionally, an ionic mechanism, recently proposed by Norton and Bullock56 for hydrogenation of ketones and imines, could be an optional explanation of transfer hydrogenation in some cases.57 Some transition metal hydrides were isolated from hydrogen transfer reactions (Figure 9), which provided evidence for the hydridic route in transfer hydrogenation.

Figure 9. Some isolated Ru hydrido complexes.
The hydride routes involve monohydridic and dihydridic pathways. Racemization experiment of α-deuterated alcohols shows that some Ru-catalyzed transfer hydrogenations proceed via the dihydride pathway. The monohydride mechanism, formally involving a hydride and a proton, applies to Rh-, and Ir-catalyzed reactions, and is suitable for most Ru-catalyzed reduction reactions.

Through the monohydride mechanism there are two pathways to transfer hydride from the metal to the carbon. One route involves the formation of a metal alkoxide followed by β-elimination to give M-H (Scheme 28, A), which happens in the inner sphere of the metal complex. Alternatively, the hydride transfer occurs in the second coordination sphere of the metal i.e. without coordination of the alcohol to the metal (Scheme 28, B), either in a concerted manner or in two discrete steps.

Scheme 28. Monohydride mechanism: inner sphere (A) and outer sphere pathway (B).

Transfer hydrogenations catalyzed by the Noyori-Ikariya’s complex catalyzed proceed in a concerted manner via a monohydride mechanism (Scheme 28, B). The reactive intermediate of amido-Ru complex has a basic center, which interacts with alcohol or amine through a hydrogen bond, thus facilitating hydrogen transfer.

Scheme 29. The mechanism of Noyori’s catalyst for transfer hydrogenation.
The proposed mechanism of Noyori’s catalyst for the transfer hydrogenation involves that the true catalyst 1 (Scheme 29) transfers the proton and the hydride from isopropanol to the ligand and metal, respectively, via a six-membered cyclic transition state to give the reactive intermediate 2. Subsequently, the 18e-ruthenium hydridocomplex transfers the proton and the hydride to oxygen and carbon of the carbonyl group, respectively, again in a concerted pathway to form the alcohol product and regenerate 1, thus complete the catalytic cycle.

There is a computational support for this mechanism and both complex 1 and 2 have been isolated and proven to be active catalysts.35

Casey studied the kinetic isotope effect in the dehydrogenation of isopropanol by Noyori’s catalyst and found the proton and hydride transfer occurred simultaneously in accordance with the mechanism proposed by Noyori.61

Concerning the mechanism of transfer hydrogenation of imines by Noyori’s catalyst, it is not simply analogous to that of transfer hydrogenation of ketones, because transfer hydrogenation of imines proceeds in an azeotropic mixture of formic acid-triethylamine, while the reaction does not occur in isopropanol.37 Recently, Bäckvall revealed that asymmetric transfer hydrogenation of imines with Noyori’s catalyst occurred in isopropanol, in the presence of a stoichiometric amount of acid.62 The imines are protonated and thereby activated by the acid prior to be reduced. It was proposed that the reduction of imines probably proceeds via an ionic mechanism, recently suggested by Norton and Bullock for hydrogenation of ketones and imines.56

### 1.2.4 Applications in ATH and Some Other Asymmetric Reactions

#### 1.2.4.1 Kinetic Resolution

**Kinetic Resolution**

The kinetic resolution of racemic mixture proceeds if the reactivity of the two enantiomers is different towards a catalytic amount of resolving reagent. An efficient separation requires the ratio of the rate constants for the two enantiomers \( k_{R}/k_{S} \) to be not less than 20-30.36

Noyori’s catalyst \((S,S-Ru)\) efficiently promoted the kinetic resolution of racemic secondary alcohols by oxidation of the \(S\)-configured enantiomer in isopropanol, giving the \(R\)-configured unreacted alcohols with high enantioselectivity (Scheme 30, up to 99% ee).63 The highly efficient kinetic resolution of unsaturated secondary alcohols occurred by using the 16e-Ru-complex under neutral condition or otherwise using the 18e-Ru-complex under basic condition.
Noyori’s catalyst has been applied in the kinetic resolution of racemic 3-hydroxymethyl-1-tetralols and 3-hydroxymethyl-1-indanols.\(^4\)

**Dynamic Kinetic Resolution (DKR)**

The theoretical yield of a single enantiomer via kinetic resolution of racemic mixture cannot exceed 50\%. An approach, known as dynamic kinetic resolution,\(^5\) overcomes the limitation of kinetic resolution by the combination of racemization and kinetic resolution. The undesired enantiomer is racemized under suitable conditions, followed by kinetic resolution, affording the desired enantiomer. A nice example of DKR is the transfer hydrogenation of a variety of cyclic α-halo ketones using Noyori’s catalyst. Vicinal bromo-, chloro-, and fluorohydrins were formed in good yields with excellent de and ee (Scheme 31).\(^2\)

The application of Noyori’s catalyst in DKR of ketones\(^6\) or imines\(^7\) via asymmetric transfer hydrogenation provides the corresponding chiral alcohols or amines in good to excellent yields with good to excellent diastereo- and enantioselectivities.

**1.2.4.2 ATH of Ketones**

Asymmetric transfer hydrogenation of a large variety of aryl alkyl ketones with Noyori’s catalyst afforded the corresponding chiral alcohols with high enantioselectivities in isopropanol or the azeotropic mixture of formic acid and triethylamine.\(^3\) The bulkiness and
the electronic properties of the alkyl group and the ring substituents affect the
diastereoselectivity and the rate of the reduction reaction. The more bulky substrates give high
selectivity at the expense of reactivity.

Acetophenone derivatives bearing an electron-withdrawing group generally undergo a
faster reaction; while electron-donating substituents make the reduction reaction more
selective (Scheme 32). The ee’s are higher when the reduction is carried out in TEAF.

Asymmetric reduction of bifunctional substrates catalyzed by TsDPEN-Ru, or TsDPEN-
Rh complexes afforded more elaborated products with high selectivities (Scheme 35, ee up to
> 99%). 2-Substituted acetophenones such as 2-chloro-, 2-cyano-, 2-azido-, 2-
nitroacetophenones, or 2-hydroxyacetophenones were efficiently reduced with a mixture
of formic acid-triethylamine giving the corresponding optically active alcohols, which are
easily converted into chiral aminoalcohols or 1,2-diol (Scheme 33).

Asymmetric reduction of ketones and further transformation of the corresponding alcohol to enantioenriched epoxides. Reagents and conditions: (i) (1). (R,R)-TsDPEN-Rh cat,
1.2. Asymmetric Transfer Hydrogenation

HCOOH/NEt$_3$, IPA, 25 °C; (2). 2 M NaOH aq, IPA, 0 °C. (ii). 0.5 mol% of [Ru(cymene)Cl$_2$]$_2$, 1 mol% of $R,R$-TsDPEN, IPA, 2.5 mol% of KOH, rt. (iii). TsCl, KOH, THF.

α-Chloro, or α-amino ketones were reduced with Rh-TsDPEN, or Ru-TsDPEN complex to give the corresponding chiral alcohols (Scheme 34, ee up to 99%), which were easily transformed into enantiomerically enriched epoxides$^{70a,b}$ or aziridines,$^{70c}$ respectively, via one- or two-pot procedures.

Noyori’s catalyst is also effective in the transfer hydrogenation of α-trimethylsilyl, or α-acetylenic ketones, giving enantiopure (S)-α-(trimethylsilyl)benzyl alcohol (Scheme 35, 98% ee)$^{71a}$ or chiral propargylic alcohols (up to 99% ee)$^{71b}$ Pyridyl ketone was reduced efficiently affording optically active pyridyl alcohols, which is a useful intermediate in medicinal chemistry and as chiral auxiliary in asymmetric synthesis.$^{72}$

\[
\begin{align*}
\text{Scheme 35. ATH of bifunctional ketones with Noyori’s catalyst} \\
\end{align*}
\]

Symmetrically or unsymmetrically substituted 1,2-$^73$ or 1,3-diketones$^{74}$ were reduced to 1,2- or 1,3-diols in the presence of Noyori’s catalyst in a mixture of formic acid-triethylamine with high diastereo- and enantioselectivity.

Generally, asymmetric transfer hydrogenation of aryl/alkyl β-keto esters to the corresponding β-hydroxyesters in the presence of Noyori’s catalyst or ephedrine-Ru complex affords high selectivity (Scheme 35).$^{75}$ However, the reduction of alkyl/alkyl β-keto esters is hampered because the Ru-amino alcohol complex is prohibited by its coordination with either of the substrate$^{75}$ or the corresponding products.$^{76}$

Asymmetric transfer hydrogenation of alkyl/alkyl ketones, which are notoriously difficult to transform into the corresponding alcohol with high enantioselectivities, has been successfully achieved with the aid of Ru phosphinooxazoline catalysts (Figure 10).$^{77}$
1.2.4.3 ATH of Imines

The asymmetric transfer hydrogenation of imines affords chiral amines, which are important precursors for the preparation of pharmaceuticals and agrochemicals. Generally, a mixture of formic acid and triethylamine is the better H-donor than IPA in these reductions. Asymmetric transfer hydrogenation of imines by using Noyori’s catalyst affords chiral amines with perfect selectivities (up to 99% ee).\(^{37}\) Recently, Bäckvall reported the transfer hydrogenation of imines using isopropanol as a hydrogen donor and acidic activation.\(^{78}\)

Imines were reduced catalyzed by rhodium-TsDPEN complex in a considerably high rate although a slightly lower enantioselectivities were obtained than those by using ruthenium complex.\(^{79}\) It was reported by Baker\(^{80a}\) and Blacker\(^{80b}\) that the reduction of imines catalyzed by a Rh-diamine complex efficiently provided chiral amines using HCOOH as a hydrogen source (Scheme 36).

Scheme 36. ATH of prochiral imines.

1.2.4.4 ATH of Alkene

Transfer hydrogenation of C=C double bond is a thermodynamically favored process, however, C=O bonds is preferentially reduced over C=C bonds. Deng\(^{81}\) has recently reported that transfer hydrogenation of C=C bonds of α,β-unsaturated ketones catalyzed by diamine-ruthenium complexes afforded saturated ketones with high chemoselectivity. The C=C double bonds have to be strongly polarized by electron-withdrawing group at α- or β- position of the double bond. In addition, a variety of unsaturated nitriles were hydrogenated with up to 89% ee, by using a slightly modified diamine ligand (Scheme 37).
1.2. Asymmetric Transfer Hydrogenation

**Scheme 37. Reduction of polarized C=C bonds.**

1.2.4.5 AH by Using Noyori’s Diamine Ru Complex

Further applications of Noyori’s catalyst in the asymmetric hydrogenation of 4-chromanones were reported very recently to give highly enantiomerically enriched alcohols (Scheme 38).82

The mechanism of this AH was rationalized as an outer sphere mechanism without metal-substrate interaction.83 The key is the generation of the cationic Ru species 2 by ionization of 1 (Scheme 39), or by the protonation of the amido complex 5.

The electrophilic Ru center reversibly accommodates an H2 molecule to form the \( \eta^2 \)-H2 complex 3.84 Deprotonation of the H2 ligand by bulk solvent generates the RuH species 4, which reduces the ketones to give enantiomerically enriched alcohol and the Ru amide 5. The Ru center donates a hydride and the NH2 ligand delivers a proton through a six-membered cyclic transition state. The step is irreversible under AH conditions. Finally, protonation at the basic nitrogen ligand of 5, regenerating 2, completes the catalytic cycle.

![Scheme 38: Asymmetric hydrogenation of 4-chromanones](image-url)
1.2. Introduction II

Scheme 39. Mechanism of AH catalyzed by Noyori’s catalyst under acidic condition. Substituents at the arene and ethylenediamine ligands are omitted for clarity.

1.2.4.6 Michael Addition Catalyzed by Noyori’s Diamine Ru Complex

Very importantly, Noyori’s complex was utilized in enantioselective C-C bond-forming reactions. The chiral amido Ru complex promoted enantioselective Michael additions of various donors including malonates, β-keto esters, 1,3-diketones, or nitroacetates to cyclic enones such as cyclopentenone or cyclohexenone or to nitroalkenes, affording the corresponding Michael adducts with high enantioselectivity up to 99% ee (Scheme 40).

Michael donors, NuH | Michael acceptors | Michael adducts
--- | --- | ---
| RO | OAr | Nu
| \( R^1 \) | \( R^2 \) | \( \text{Nu} \)
| \( R^1 \) | \( R^2 \) | \( \text{Ar} \)

Scheme 40. Asymmetric Michael addition of 1,3-dicarbonyl compounds or nitroacetate to \( \alpha,\beta \)-unsaturated ketones or nitroalkenes
Based on the mechanism of ATH using the amido Ru complex, those reactions are believed to proceed via an α-metalated structure A (Scheme 41) formed upon deprotonation of the acidic substrate. Corresponding Ru and Ir complex have been isolated and characterized by X-ray diffraction analysis. Nucleophilic attack onto the α,β-unsaturated carbonyl compound via a cyclic transition state B generates the product.

In summary, the bifunctional Ru diamine type complexes have been originally developed for asymmetric transfer hydrogenation of ketones and imines, and now they are successfully applied to ATH of activated C=C double bonds, AH of ketones and imines, and enantioselective C-C bond forming reaction.
1.3 Results and Discussion

Introduction

Amongst various reducing methods transfer hydrogenation reaction has drawn much attention and was developed extensively since the 1920s because of its operational simplicity and easy availability of hydrogen source.\(^{88}\) Ruthenium-catalyzed asymmetric transfer hydrogenation is a most attractive field and the method has been a key strategy to access highly enantiomerically enriched alcohols.\(^{89}\) Up to now, ruthenium-amido complexes, developed by Noyori and Ikariya (Scheme 42, \(R,R\)-Ru or \(S,S\)-Ru, namely, Noyori’s catalyst),\(^{88}\) catalyze ATH giving the corresponding alcohols with highest enantioselectivity.\(^{35a}\)

Asymmetric transfer hydrogenation of alkyl/alky ketone using TsDPEN-Ru (\(R,R\)-Ru or \(S,S\)-Ru) catalyst has not gained much success. Reduction of \(\alpha,\alpha\)-disubstituted-\(\beta\)-keto ester has not been attempted. We have expanded the scope of reaction to ATH of alkyl/alkyl ketones (\(\alpha,\alpha\)-disubstituted-\(\beta\)-keto ester) using Noyori’s catalyst to give the corresponding alcohols with high enantioselectivities in good to excellent yields (Scheme 42). Herein, we describe the synthesis of optically active \(\alpha\)-fluoro-\(\beta\)-hydroxy esters or amide via ATH of racemic \(\alpha\)-fluoro-\(\beta\)-keto esters or amide using Noyori’s catalyst.

![Scheme 42 ATH of \(\alpha\)-fluoro-\(\beta\)-keto esters using Noyori’s catalyst.](image)

1.3.1 Preparation of Catalysts

Preparation of Ru-Complex for Transfer Hydrogenation

The purpule 16e-Ru-complex (\(R,R\)-Ru or \(S,S\)-Ru) catalyzes the hydrogen transfer reaction under very mild conditions: at room temperature, in 2-propanol, while no other additive (base) is required. However, the brown 18e-ruthenium-complex shown in Figure 11 requires basic conditions. The desired product with fluorine in the \(\alpha\)-position of the ester might eliminate HF under basic condition to form a defluorinated \(\beta\)-keto ester (Scheme 43). Therefore, in order to avoid the possibility of HF-elimination, the milder reaction conditions
under catalysis of the 16e-Ru(II)-complex were utilized for the transfer hydrogenation of fluorinated β-keto esters.

![Catalyst precursor](image)

Figure 11. The 18e-Ruthenium complex-used as the catalyst precursor.

![Scheme 43](image)

Scheme 43. The possible HF-elimination under base condition

Both enantiomerically pure 16e-ruthenium-complexes were easily prepared and isolated as reported. The ligand \( R,R-\text{TsDPEN} \) or \( S,S-\text{TsDPEN} \) reacted with \([\text{RuCl}_2(\eta^6-\text{p-cymene})]_2\) to afford the desired complex (Scheme 44).

![Scheme 44](image)

Scheme 44. Preparation of 16e-Ru-complex (\( R,R-\text{Ru} \))

An achiral ruthenium 16e-complex (Scheme 45, **non-chiral-Ru**) was synthesized by the treatment of \([\text{RuCl}_2(\eta^6-\text{p-cymene})]_2\) with monotosylated 1,2-diaminoethane, similar to the preparation of \( R,R-\text{Ru} \). Under catalysis with **non-chiral-Ru**, reduction of fluorinated β-keto ester gives the corresponding racemic mixture of fluorinated β-hydroxy ester.

![Scheme 45](image)

Scheme 45. Preparation of non-chiral ruthenium complex.
Preparation of Ti(TADDOLatoCl₂) (R,R-Ti or S,S-Ti) Asymmetric for Electrophilic Fluorination

The fully characterized Ti(TADDOLatoCl₂) complex (Figure 12, R,R-Ti) was developed and applied in asymmetric electrophilic fluorination of ß-keto esters in our group. It also catalyzes some other asymmetric reactions such as halogenation (Cl, Br), hydroxylation and sulfonylation. The two enantiomeric complexes (R,R-Ti and S,S-Ti, Figure 12) were prepared according to the reported procedure and were used for the synthesis of a few enantiomerically enriched α-fluoro-ß-keto esters and α-chloro-ß-keto esters.

![Figure 12. Ti-complex for electrophilic fluorination](image)

1.3.2 Preparation of Racemic and Optically Active Halogenated Keto Esters or Amides and the Corresponding Racemic Halogenated Hydroxy Esters or Amide

Fluorinated Substrate and the Corresponding Alcohols

A series of racemic α-fluoro-ß-keto esters or amides were prepared, in the presence of a catalytic amount of CpTiCl₃ or TiCl₄ via electrophilic fluorination in moderate to good yields (Table 3, S1-S10, 57-97% yield). Most of the fluorination reactions proceeded smoothly and cleanly, however, fluorination of 2-acetylbutyrolactone afforded the expected product S9a accompanied by a trace of 2-fluoro-2-(fluoroacetyl)butyrolactone S9b, detected by ¹⁹F NMR in the crude product (Scheme 46).

![Scheme 46. Fluorination of 2-acetylbutyrolactone](image)

The corresponding racemic hydroxy derivatifs were generated as a mixture of diastereoisomers by reduction reaction with NaBH₄ or a mixture of R,R-Ru and S,S-Ru (1:1). The results are collected in Table 3. Reduction of fluorinated ß-keto esters with NaBH₄ shows some diastereoselectivity, whereby the diastereomeric ratios (less polar isomer:more polar isomer) were determined by ¹⁹F NMR of the crude product mixture. The modestly hindered
1.3. Results and Discussion

Chain substrates (S1 and S2) were reduced to the corresponding alcohols as a mixture with a dr of 1:1; while the reductions of the more sterically hindered ß-keto esters (S3-S6) gave some diastereoselectivities. On the other hand, a series of cyclic fluorinated ß-keto esters were reduced with a diastereoselectivity up to 1:10 (entry 10, P10). The 1:1 mixture of R,R-Ru and S,S-Ru (1:1) catalyzed transfer hydrogenation affording fluorinated ß-hydroxy esters with high diastereoselectivity. It was a surprise, for example, to observe P8 with dr 50:1. We examined the reduction of a ß-keto ester (S9) under both condition. The diastereomeric ratio of the product was switched from 1:2.5 to 2:1 in the presence of the racemic mixture of Ru-complexes. However, the asymmetric transfer hydrogenation of S9 in the presence of R,R-Ru or S,S-Ru gives a 1:1 mixture of diastereoisomers. We do not have a plausible explanation for the strange selectivity under catalysis with a 1:1 mixture of R,R-Ru and S,S-Ru.

α-Halogenated (F, Cl) or α-Hydroxy Substrates and the Corresponding Alcohols

Some racemic α-chloro-ß-keto esters were prepared under catalysis of CpTiCl3 or TiCl4 by electrophilic chlorination according to our method in satisfactory yields.

Racemic α-hydroxy-ß-keto esters or amides were prepared under catalysis of AlCl3 by electrophilic hydroxylation of ß-keto esters or amides in good yield. The corresponding reduced ß-hydroxy esters or amides were generated by classical reduction method by NaBH4 in moderate to good yields (Table 4). The diastereomeric ratio was determined by integration of ¹H NMR spectrum of the crude product, except for P13 where it was calculated after isolation of the diastereoisomers.

Preparation of Some Optically Active Fluorinated or Chlorinated ß-Keto Esters

Some optically active fluorinated or chlorinated ß-keto esters were prepared by asymmetric electrophilic fluorination according to our known method (Table 5). The enantiomerically enriched fluorinated or chlorinated ß-keto esters were initially used to investigate the asymmetric transfer hydrogenation. Furthermore, some of them have been used for the determination of the absolute configuration by further transformation and attachment of a chiral moiety of known configuration. This will be discussed later.

The enantioselective electrophilic fluorinations were performed in the presence of a catalytic amount of Ti(TADDOLato)Cl2 i.e. R,R-Ti or S,S-Ti, using FTEDA as a fluorinating reagent in acetonitrile at room temperature, as reported by our group. The electrophilic chlorination reactions were carried out using NCS as a chlorinating reagent.
### 1.3. Synthesis of α-Fluoro-β-hydroxy Compounds

Table 3. Preparation of racemic α-fluoro-β-keto esters, -amides and the corresponding racemic fluorinated β-hydroxy esters or amides

<table>
<thead>
<tr>
<th>entry</th>
<th>fluorinated β-keto esters or amides (S)</th>
<th>yield (%)</th>
<th>fluorinated β-hydroxy esters or amides (P)</th>
<th>yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S1</td>
<td>97</td>
<td>P1</td>
<td>90</td>
<td>1:1.3</td>
</tr>
<tr>
<td>2</td>
<td>S2</td>
<td>66</td>
<td>P2</td>
<td>34</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>S3</td>
<td>82</td>
<td>P3</td>
<td>38</td>
<td>1:3</td>
</tr>
<tr>
<td>4</td>
<td>S4</td>
<td>88</td>
<td>P4</td>
<td>90</td>
<td>1:1.3</td>
</tr>
<tr>
<td>5</td>
<td>S5</td>
<td>57</td>
<td>P5</td>
<td>76</td>
<td>3:1</td>
</tr>
<tr>
<td>6</td>
<td>S6</td>
<td>87</td>
<td>P6</td>
<td>95</td>
<td>3:1</td>
</tr>
<tr>
<td>7</td>
<td>S7</td>
<td>70</td>
<td>P7</td>
<td>89</td>
<td>3:1</td>
</tr>
<tr>
<td>8</td>
<td>S8</td>
<td>86</td>
<td>P8</td>
<td>90(^e)</td>
<td>50:1(^e)</td>
</tr>
<tr>
<td>9</td>
<td>S9</td>
<td>66</td>
<td>P9</td>
<td>70</td>
<td>1:2.5</td>
</tr>
<tr>
<td>10</td>
<td>S10</td>
<td>96</td>
<td>P10</td>
<td>97</td>
<td>1:10</td>
</tr>
</tbody>
</table>
1.3. Results and Discussion

Unless otherwise noted, the reactions were performed, in the presence of CpTiCl₃ (5 mol%) or TiCl₄ (5 mol%) F-TEDA (1.16 eq) in acetonitrile at room temperature; isolated yields by flash chromatography; Unless otherwise noted the reactions were performed in the presence of NaBH₄ (1.1 eq) in methanol at -20 °C; Dr determined by ¹⁹F NMR of crude product; The reaction were performed in the presence of a mixture of R,R-Ru and S,S-Ru (1:1) (1 mol%) in 2-propanol at room temperature.

Table 4. Preparation of racemic α-chloro-β-keto esters α-hydroxy-β-keto amides and the corresponding racemic α-chloro-β-hydroxy esters or α,β-dihydroxy amides

<table>
<thead>
<tr>
<th>entry</th>
<th>chlorinated β-keto esters or amides (S)</th>
<th>yield (%)</th>
<th>chlorinated β-hydroxy esters or amides (P)</th>
<th>yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S11</td>
<td>90</td>
<td>P11</td>
<td>79</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>S12</td>
<td>75</td>
<td>P12</td>
<td>90</td>
<td>1:3</td>
</tr>
<tr>
<td>3</td>
<td>S13</td>
<td>94</td>
<td>P13</td>
<td>75</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>S14</td>
<td>70</td>
<td>P14</td>
<td>80</td>
<td>1:1</td>
</tr>
<tr>
<td>5</td>
<td>S15</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>S16</td>
<td>84</td>
<td>P16</td>
<td>90</td>
<td>2:1</td>
</tr>
</tbody>
</table>

Unless otherwise noted, the reactions were performed, in the presence of CpTiCl₃ (5 mol%) or TiCl₄ (5 mol%) NCS (1.16 eq) in acetonitrile at room temperature; isolated yields by flash chromatography; Unless otherwise noted, the reactions were performed in the presence of NaBH₄ (1.1 eq) in the methanol at -20 °C; Dr determined by integration of the ¹H NMR spectrum of the crude product; The reaction were performed in the presence of AlCl₃ (5 mol%) oxaziridine (1.1 eq) in toluene at room temperature; Dr estimated after isolation of the diastereoisomer.
1.3. Synthesis of α-Fluoro-β-hydroxy Compounds

Table 5. Preparation of optically active α-fluoro-β-keto esters, amides or α-chloro-β-keto esters. 

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>F-or Cl-reagents</th>
<th>product</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-Ti</td>
<td>F-TEDA</td>
<td>S1</td>
<td>81</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-Ti</td>
<td>F-TEDA</td>
<td>S2</td>
<td>92</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>(S,S)-Ti</td>
<td>F-TEDA</td>
<td>S10</td>
<td>79</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>(R,R)-Ti</td>
<td>F-TEDA</td>
<td>S5</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>(R,R)-Ti</td>
<td>F-TEDA</td>
<td>S6</td>
<td>89</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-Ti</td>
<td>NCS</td>
<td>S12</td>
<td>82</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>(R,R)-Ti</td>
<td>NCS</td>
<td>S13</td>
<td>94</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

*Unless otherwise noted, the reactions were performed, in the presence of Ti(TADDOLato)Cl₂ (5 mol%) F-TEDA or NCS (1.16 eq) in acetonitrile at room temperature; \(^b\) Isolated yields by flash chromatography; \(^c\) Determined by chiral HPLC; \(^d\) Ee not determined, optical rotation was measured \([\alpha]_{D}^{20} = -5.08 \pm 0.05\) (c = 1.23, MeOH).

1.3.3 Preliminary Investigation on the Transfer Hydrogenation (Reduction of Optically Active α-Fluoro-α-methyl-3-oxo-phenylpropanoate (S1, 40% ee)

Because aryl/alkyl ketones are usually well suited substrates for transfer hydrogenation reactions, we initially speculated that ethyl α-fluoro-α-methyl-3-oxo-phenylpropanoate (S1, 40% ee), prepared directly via asymmetric fluorination, would be an optional model substrate.
Complete conversions were achieved with catalyst loading of 1 mol%, using isopropanol as hydrogen source (Table 6).

Table 6. Transfer hydrogenation of ethyl α-fluoro-α-methyl-3-oxo-phenylpropanoate (with 40% ee).a

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R,R-Ru</td>
<td>95</td>
<td>1:11</td>
<td>23, 47</td>
</tr>
<tr>
<td>S,S-Ru</td>
<td>91</td>
<td>1:7</td>
<td>80, 32</td>
</tr>
<tr>
<td>Non-chiral-Ru</td>
<td>98</td>
<td>1:9</td>
<td>15, 65</td>
</tr>
<tr>
<td>rac-Ru [a]</td>
<td>99</td>
<td>1:8</td>
<td>17, 67</td>
</tr>
</tbody>
</table>

[a] Unless otherwise specified, the reactions were carried out using 0.5 mmol of substrates S1 (40% ee), with 1 mol% of catalyst loading at room temperature in 20 h; [b] isolated yields after chromatography; [c] Dr determined by $^{19}$F NMR spectroscopic analysis; [d] Ee determined by chiral HPLC analysis; [e] rac-Ru is a mixture of R,R-Ru and S,S-Ru (1:1).

Transfer hydrogenation of S1 catalyzed by R,R-Ru afforded fluorinated β-hydroxy ester (P1) with good diastereoselectivity (entry 1, dr = 1:11), but with poor enantioselectivity (23% and 47% ee). To our surprise, the utilization of the opposite enantiomer of the catalyst (S,S-Ru) resulted in the same major diastereoisomer (entry 2, dr = 1:7), with moderate enantioselectivity (80% and 32% ee). It should be pointed out that the two enantiomeric ruthenium complexes afforded the same major diastereoisomer of the fluorinated β-hydroxy esters, however, with inversed enantioselectivities, as shown by chiral HPLC by comparing with the corresponding racemic mixture.

In the presence of the non-chiral Ru complex or rac-Ru (a 1:1 mixture of R,R-Ru and S,S-Ru), the same major diastereoisomer (with poor ee) of the fluorinated β-hydroxy ester was formed with dr = 1:9 or 1:8, respectively. The moderate enantioselectivities were obviously transferred from the chiral substrate (S1 with 40% ee).

Compared to the diastereoselectivity in the reduction reaction with NaBH₄ (dr = 1:1.3), a better diastereoselectivity was obtained through the hydrogen transfer reaction catalyzed by Ru. There are several possible reasons explaining these different diastereoselectivities: The hydride source (Ru-H) is more sterically hindered than NaBH₄, the strongly electronegative fluorine atom of the substrate interacts with the ligand, or a CH/π interaction exists between the cymene and the phenyl of the substrate. The possibilities effect of fluorine, in particularly, will be examined in the following experiments.
1.3.4 Investigation of the Asymmetric Transfer Hydrogenation of Racemic α-Halo-β-keto Esters

Racemic ethyl α-fluoro-α-methyl-3-oxo-phenylpropanoate (SI) was reduced in the presence of 1 mol% of $\text{R,R-Ru}$ or $\text{S,S-Ru}$ affording the corresponding alcohol P1 with $\text{dr} = 1:10$ or $1:9$, respectively (Table 7, entries 1, 2). Poor enantioselectivities in the range of 1-46% ee are obtained. Similar to the reduction of optically active SI with 40% ee, opposed enantiomers were generated with the enantiomeric Ru complexes, as determined by chiral HPLC.

In order to prove the hypothesis of a possible interaction of the fluorine atom of the substrate with the ligand, the racemic chlorinated β-keto esters (S11, S12, S14) were reduced under the same condition (Table 7). Asymmetric reduction of chlorinated substrates (S11 and S14) structurally similar to fluorinated β-keto ester SI, gave the same major isomer when using both enantiomeric Ru complexes. A low diastereoselectivity was obtained as compared to that of reduction of fluorinated β-keto ester (entry 2, 1:2, entry 3, 1:3 or 1:8). These results show that the fluorine atom does not have any peculiar effect on the selectivity of the reduction reaction.

Table 7. Asymmetric transfer hydrogenation of racemic α-halo-β-keto esters.$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>condition $^b$</th>
<th>yield (%)$^c$</th>
<th>dr$^d$</th>
<th>ee (%)$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SI</td>
<td>P1</td>
<td>A</td>
<td>93</td>
<td>1:10</td>
<td>38, 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>85</td>
<td>1:9</td>
<td>46, 1</td>
</tr>
<tr>
<td>2</td>
<td>S11</td>
<td>P11</td>
<td>A</td>
<td>10$^g$</td>
<td>1:2</td>
<td>42, 52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>8$^g$</td>
<td>1:2</td>
<td>33, 39</td>
</tr>
<tr>
<td>3</td>
<td>S14</td>
<td>P14</td>
<td>A</td>
<td>48$^g$</td>
<td>1:3</td>
<td>92, 36$^f$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>8$^g$</td>
<td>1:8</td>
<td>78, 73</td>
</tr>
<tr>
<td>4</td>
<td>S12</td>
<td>P12</td>
<td>A</td>
<td>93</td>
<td>1:1</td>
<td>94, 96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>96</td>
<td>1:1</td>
<td>93, 93</td>
</tr>
<tr>
<td>5</td>
<td>S12</td>
<td>P12</td>
<td>A</td>
<td>77</td>
<td>1:1</td>
<td>92, 87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>53</td>
<td>1:1</td>
<td>93, 87</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise specified, the reactions were carried out using 0.5 mmol of substrates with 1 mol% of catalyst in 2-3 mL of isopropanol at room temperature in 20 h; $^b$ Condition A is under catalysis of $\text{R,R-Ru}$, while condition B is under catalysis of $\text{S,S-Ru}$; $^c$ Isolated yields after flash chromatography; $^d$ Determined by $^{19}$F NMR or $^1$H NMR spectroscopic analysis of crude mixture; $^e$ Determined by chiral HPLC analysis; $^f$ Ee was not determined because of impurity; $^g$ Catalyst loading was up to 2 mol%.
Further investigation of a possible fluorine effect by reduction of alkyl/alkyl \( \beta \)-keto esters (entries 4, 5, S2, S12) demonstrates that the diastereoselection of the reaction is not enhanced by \( \alpha \)-substitution with a fluorine or chlorine atom because both corresponding substrates S2 and S12 were hydrogenated to the corresponding alcohols with no diastereoselectivity (\( \text{dr} = 1:1 \)). However, the results show that the structure of the substrate is crucial to the diastereoselection of the reduction reaction. The possible and reasonable explanation is the CH/\( \pi \) interaction\(^{92}\) between the cymene and the phenyl of the substrate, which stabilizes the transition state to provide high selectivity in the case of the reduction of S1, S11 and S14. On the other hand, reduction of S2 or S12 gives 1:1 diastereoselection due to the absence of CH/\( \pi \) interaction.

It is worth pointing out that the highly diastereoselective formation of alcohols is accompanied by low enantioselectivities (Table 7, entries 1-3), while 1:1 diastereomeric mixture displaying ee’s (entries 4 and 5, 87-96% ee). The reason is that racemic starting material contains a non epimerizable quaternary carbon center. If 100% conversion of the reaction is reached, high enantioselection can be reached by the corresponding alcohols if the diastereoselectivity is low. Otherwise, the high enantioselective formation of product could be obtained via kinetic resolution of the racemic substrate. Without any doubt, the enantioselection in the transfer hydrogen reaction is ascribed to the control by the catalyst.

It is worth noting that all the yields of the asymmetric reduction of \( \alpha \)-chloro-\( \beta \)-keto esters are quite low, while those of the reduction of \( \alpha \)-fluoro-\( \beta \)-keto esters are much higher. Presumably, the chlorine substituent of the \( \beta \)-keto esters, or the corresponding \( \alpha \)-chloro-\( \beta \)-hydroxy ester, coordinates to the Ru complex, this leading to partial deactivation.\(^{93}\) This is not the case for the corresponding fluorinated substrates.

There is another NMR experimental support for the unusual diastereoselection in the reduction of the aryl/alkyl ketones. The reaction mixture of S1 and \( R,R \)-Ru in isopropanol was studied by an NOE NMR experiment. A strong NOE between fluorine and a proton of the phenyl group was detected (Scheme 47, S1). This intramolecular interaction between the fluorine atom and the ortho hydrogen of the phenyl somewhat fixes the conformation, thus leading to the formation of the same major diastereoisomer, no matter which enantiomeric form of the catalyst is used. On the other hand, in the case of alkyl/alkyl keto esters the hydrogen bond between the fluorine and the hydrogen of the alkyl group is not a dominant factor for the selectivity of the reaction (Scheme 47, S2).

![Scheme 47. The NOE in the different \( \beta \)-keto esters](image-url)
1.3. Synthesis of α-Fluoro-β-hydroxy Compounds

Additionally, we surveyed the transfer hydrogenation of α-hydroxy keto ester or amide (Scheme 48). We did not obtain the expected dihydroxy products, only recovered the substrate, probably due to the deactivation of the catalyst by coordination of the hydroxyl group with Ru.93

Scheme 48. Attempt on the transfer hydrogenation of α-hydroxy keto ester and amide

In summary, the asymmetric reductions of aryl/alkyl fluorinated β-keto esters afford good diastereoselectivities and low enantioselectivities, most probably due to the CH/π interaction with the catalyst. Reductions of alkyl/alkyl fluorinated β-keto esters afford the corresponding alcohols as a 1:1 diastereomeric mixture with high enantioselectivities.

1.3.5 Further Investigation of ATH of α-Fluoro-β-keto Ester - the Possibility of Kinetic Resolution

We found that the reduction of alkyl/alkyl β-keto esters gave the corresponding alcohols with high enantioselectivity, albeit with 1:1 diastereoselectivity. If the two enantiomers of the β-keto ester containing a quaternary carbon can be discriminated by the catalyst and have different reaction rates, then kinetic resolution can be obtained during reduction. The slow reacting enantiomer will be left as an enantiomerically enriched fluorinated β-keto ester, while the more active enantiomer will be reduced with both high diastereo- and enantioselectivity. Based on this assumption, an alkyl/alkyl fluorinated β-keto ester (S3) was subjected to transfer hydrogenation, in the presence of R,R-Ru, at room temperature (Table 8). The reduction reaction was monitored by removing a small amount of the reaction mixture every two or three hours. The reaction conversion and dr of the corresponding product was determined by $^{19}$F NMR, and the ee was determined by chiral HPLC. The results are summarized in Table 8. We found that the unreacted substrate was still a racemic mixture and the dr of the corresponding product was 1:1 during the whole process (conversion from 0-42%). This shows that the two enantiomers of the substrate react nearly at the same rate, i.e. the Ru-complex can not discriminate between the two enantiomers of the substrate. The enantioselectivities of the fluorinated β-hydroxy esters are high, which further proves that the fluorinated β-keto ester and the corresponding alcohol do not deteriorate the catalyst species. It should be mentioned that the ee’s value of the product measured by HPLC was not very accurate because the concentration of sample was too low to obtain a precise integration. However, the ee’s values of the hydrogenated products are in the range of 80-99%. We also examined the reduction of S3 under catalysis with S,S-Ru and the similar results were obtained.
Table 8. Asymmetric transfer hydrogenation of phenyl 2-fluoro-2-methyl-3-oxo-pentanoate (S3).

<table>
<thead>
<tr>
<th>entry</th>
<th>time (h)</th>
<th>conv. (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>substrate (S3) ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>product (P3) dr&lt;sup&gt;d&lt;/sup&gt; (ee %)&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1:1 (&gt;99, 60)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>14</td>
<td>0</td>
<td>1:1 (&gt;99, 77)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>35</td>
<td>0</td>
<td>1:1 (&gt;99, 77)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>37</td>
<td>0</td>
<td>1:1 (81, &gt;99)</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>42</td>
<td>0</td>
<td>1:1 (93, 87)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The reactions were performed with 0.26 mmol substrate 0.7 mol% of catalyst (R,R-Ru) in 2 mL of 2-propanol at room temperature. <sup>b</sup> Conversion was determined by 19F NMR spectrum of the crude mixture. <sup>c</sup> Ee determined by chiral HPLC. <sup>d</sup> Dr determined by 19F NMR spectrum of the crude mixture. <sup>e</sup> The ee’s value is not very accurate because the concentration of the product is very low compared to the unreacted substrate. Sometimes, the minor enantiomer could not be detected by HPLC, however, the values are in the range of 80–99%.

On the basis of the foregoing observation we come to the conclusion that the fluorinated alkyl/alkyl β-keto esters are appropriate substrates toward asymmetric transfer hydrogenation under the attempted reduction condition. These are due to a strong catalyst control of the reaction. Enantioselectivities up to 99% can be achieved.

1.3.6 The Scope of the Asymmetric Transfer Hydrogenation of Racemic α-Fluoro-β-keto Esters or Amides

Since the alkyl/alkyl α-fluoro-β-keto esters were reduced to stable fluorinated β-hydroxy esters with high enantioselectivities in good yields, we subsequently extended the scope of this reaction to other linear chain or cyclic α-fluoro-β-keto esters and amides and the results are summarized in Table 9.

The phenyl α-fluoro-β-keto ester (S3) was reduced to the corresponding β-hydroxy ester (P3) in the presence of R,R-Ru (condition A) or S,S-Ru (condition B) in isopropanol at room temperature, with excellent enantioselectivities (up to 99% ee) and 1:1 diastereomeric ratio. However, the yields were quite low (entry 1, 37% or 7%) because of partial ester hydrolysis as indicated by the formation of phenyl which was accompanied by another fluorinated species, detected by 19F NMR. This is, however, too volatile to be isolated and purified. Even
when the catalyst loading was increased up to 2 mol%, the yield of the reduction reaction did not improve. Presumably, the coordination of the phenol generated in situ with the Ru-complex shuts down the catalytic cycle. This deactivation of the catalyst did not happen in the case of another aryl ester (S4). 4-Methoxyphenyl α-fluoro-β-keto ester was smoothly hydrogenated with good enantioselectivities (entry 2, P4 with 92% and 88% ee; or with 93% and 88% ee) with dr of 1:1 in high yields. Subsequently, the more bulky β-keto ester S5 was subject to asymmetric transfer hydrogenation affording the corresponding α-fluoro-β-hydroxy ester (P5) with dr = 1:1 in quite high yields (entry 3). Unfortunately, only the ee’s of the more polar diastereomer of the product could be determined (91% ee, or 92% ee). Asymmetric transfer hydrogenation of the sterically hindered 2,4,5-trisopropylphenyl fluorinated β-keto ester S6 with complex R,R-Ru gave the products in a diastereomeric ratio of 1:1:8. On the other hand, catalyst S,S-Ru led to the desired product with 1:7:1 diastereomeric ratio. This is the only case where a reversed diastereomeric ratio of the fluorinated β-hydroxy ester was obtained upon reduction with the two enantiomers of the Ru complex. Most probably, the steric bulk of the ester group plays an important role. Unfortunately, the ee’s of P6 could not be determined.

We have surveyed the reduction reaction of a range of cyclic β-keto esters and amides. The bulky cyclic tert-butyl 1-fluoro-2-oxo-cyclopentanecarboxylate S7 was reduced to give the same diastereoselection (dr = 2:1) and good yields (entry 5, P7, dr = 2:1). The less polar diastereoisomer has moderate ee (entry 5, 46% ee, or 45% ee), while the more polar diastereoisomer has perfect enantioselectivity (entry 5, >99% ee). We also found that the enantioselective reduction of the six-membered cyclic β-keto ester S8 afforded the desired fluorinated β-hydroxy ester with high enantioselectivity (entry 6, ee up to >99%) and 1:1 diastereomeric ratio in satisfactory yields. Asymmetric transfer hydrogenation of the γ-lacton S9 provided the corresponding highly enantiomerically pure fluorohydrin P9 in high yields (entry 7, 86-96% ee). The diastereomeric ratio is 1:1:1 or 1:1:2. Finally, an α-fluoro-β-keto lactam S10 was hydrogenated to the corresponding α-fluoro-β-hydroxy lactam with satisfactory results (entry 8, P10, dr = 6:1, 95%, 96% ee, in 57% yield; or dr = 2:1, 95%, 99% ee, in 76% yield).

The diastereomeric products are obtained in nearly enantiomerically pure form by flash chromatography, except for the two diastereomers of P2 and P6 which can only be partly separated. Moreover, it is hard to separate the diastereomers of P3 and P4. As shown by the chromatograms of Figure 13 the enantiomerically pure fluorinated β-hydroxy lactams (A, B, C, and D) may be obtained via ATH by choosing the corresponding Ru-amido complex as a catalyst followed by chromatography of the corresponding diastereoisomers.
Table 9. Asymmetric transfer hydrogenation of various racemic α-fluoro-β-keto esters and amides.

\[
\text{R}_1 \xrightarrow{\text{R,\text{R-Ru} or S,\text{S-Ru}}} \text{R}_2 \xrightarrow{\text{PrOH}} \text{R}_3
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>condition</th>
<th>yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S3</td>
<td>P3</td>
<td>A</td>
<td>37</td>
<td>1:1</td>
<td>99, 85</td>
</tr>
<tr>
<td>2</td>
<td>S4</td>
<td>P4</td>
<td>B</td>
<td>9</td>
<td>1:1</td>
<td>99, 99</td>
</tr>
<tr>
<td>3</td>
<td>S5</td>
<td>P5</td>
<td>A</td>
<td>81</td>
<td>1:1</td>
<td>n.d., 91</td>
</tr>
<tr>
<td>4</td>
<td>S6</td>
<td>P6</td>
<td>B</td>
<td>86</td>
<td>1.7:1</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>S7</td>
<td>P7</td>
<td>A</td>
<td>80</td>
<td>2.1:1</td>
<td>46, &gt;99</td>
</tr>
<tr>
<td>6</td>
<td>S8</td>
<td>P8</td>
<td>B</td>
<td>81</td>
<td>1:1</td>
<td>85, &gt;99</td>
</tr>
<tr>
<td>7</td>
<td>S9</td>
<td>P9</td>
<td>A</td>
<td>95</td>
<td>1:1.1</td>
<td>96, 87</td>
</tr>
<tr>
<td>8</td>
<td>S10</td>
<td>P10</td>
<td>B</td>
<td>76</td>
<td>2:1</td>
<td>95, 99</td>
</tr>
</tbody>
</table>

*Unless otherwise specified, the reactions were carried out using 0.5 mmol of substrates with 1 mol% of catalyst in 2-3 mL of isopropanol at room temperature 20 h; Condition A is under catalysis of R,\text{R-Ru}, while condition B is under catalysis of S,\text{S-Ru}; Isolated yields after chromatography; Catalyst loading up to 2 mol%. Dr determined by \textsuperscript{19}F NMR spectroscopic analysis of the crude mixture; Ee determined by chiral HPLC analysis.
In summary, the enantiomerically enriched fluorinated β-hydroxy esters or amides can be obtained by asymmetric transfer hydrogenation of racemic fluorinated β-keto esters or amides. Since the asymmetric transfer hydrogenation of racemic α-fluoro-β-keto esters has been investigated to give excellent enantioselectivities, it is essential to combine the method with asymmetric electrophilic fluorination of β-keto esters to generate the desired optically active α-fluoro-β-hydroxy esters because the two stereogenic centers are easily controlled by choice of the appropriate enantiomeric form of the catalyst. That is, \( S,S\)-Ti- or \( R,R\)-Ti-catalyzed asymmetric electrophilic fluorination of β-keto esters affords the \( R \) or \( S \) quaternary stereocenter, respectively.\[^{94}\] This has no effect on the derivation of the tertiary stereogenic center generated via asymmetric transfer hydrogenation, i.e., \( R,R\)-Ru- or \( S,S\)-Ru-catalyzed transfer hydrogenation generates the \( R \) or \( S \) configured alcohol.\[^{35b,63}\] Actually, we have combined the two asymmetric catalytic reaction to obtain an enantiomerically pure α-fluoro-β-hydroxy amide that to served for the determination of the absolute configurations of the two stereogenic carbon centers.\[^{94}\]

### 1.3.7 Determination of the Absolute Configuration of a Derivative of Fluorinated β-Hydroxy Ester or Amide

Since our group originally developed the asymmetric electrophilic fluorination, it was essential to determine the absolute configuration of the corresponding quaternary stereocenter connected to fluorine. The absolute configuration of an unknown stereocenter can be determined by several methods. One is to transform the molecule into a compound of known configuration and compare the values of the optical rotation. Another possibility is to connect the new compound to a chiral compound of known configuration and determine the desired
absolute configuration by internal comparison when an X-ray crystal structure of the new derivative is accessible.

Since the asymmetric transfer hydrogenation provides highly enantiomerically pure fluorinated β-hydroxy ester, one simple condensation reaction between the hydroxyl group of the fluorinated ester and a chiral enantiomerically pure acid or acyl chloride with a known chiral carbon center will easily afford a derivative. Once a single crystal of the derivative is obtained, absolute configuration will be determined by X-ray diffraction. Depending on the basic rule, a transformation of our hydrogenated product was attempted. A fluorinated β-hydroxy amide (Scheme 49, S10, 53% ee), which was obtained by enantioselective fluorination catalyzed by S,S-Ti, was reduced by asymmetric transfer hydrogenation to give highly enantiomerically pure fluoro-hydroxy amide P10 (major isomer with 96% ee, dr = 2:1). The major diastereoisomer was separated by flash chromatography and reacted with (S)-(+) 10-camphorsulfonyl chloride to provide the corresponding derivative (Scheme 49, 17).

Scheme 49. Synthesis of a derivative of α-fluoro-β-hydroxy amide.

Figure 14. Ortep representation of α-fluoro-β-hydroxy amide’s derivative 17. Selected bond length (Å): C10-F1 1.404. Selected torsion angles (°): F1-C10-C11-O3(R) 65.1, F1-C10-C9=O2 82.1, F1-C10-O2-N 100.8.
Single crystals were grown in CD₂Cl₂-pentane and the X-ray diffraction study shows the R-configuration of the center that was generated by S,S-Ti-catalyzed fluorination, whereas S,S-Ru-catalyzed transfer hydrogenation gives the R-configuration for the alcohol center. The X-ray structure of the sulfonyl-derivative is shown in Figure 14. The configurations of the two stereogenic centers generated by asymmetric catalysis are as expected. Concerning the stereogenic center produced by asymmetric fluorination, our group did computational and crystallographic studies of the Ti(TADDOLato) complexes and came to the conclusion the S,S-Ti-catalyzed fluorination leads to the R-configuration. Noyori described that R,R-Ru-catalyzed asymmetric transfer hydrogenation of ketones generates the alcohol with R-configuration.

The absolute configuration of 17 was unambiguously determined by X-ray diffraction, which provides a strong proof on the origin of enantioselectivity in the Ti-catalyzed fluorination. We are applying this knowledge to devise the synthesis of new ligand for enantioselective electrophilic fluorination with modified steric and electronic properties.

An enantiomerically enriched fluorinated β-hydroxy ester P9 with two chiral stereogenic center, generated via ATH of a fluorinated β-keto ester, was converted to derivative 18 by reaction with (S)-camphanic acid chloride as shown in Scheme 50.

Scheme 50. A derivative 18 of a reduced fluorinated product.

Figure 15. Ortep representation of of 18. Selected bond length(Å): C-F 1.410. Selected torsion angles (°): F1-C2-C5-O3(R) 62.2, F-C2-C1=O1 82.3, F-C2-C1-O2 94.0.
Single crystals were grown by diffusion of pentane to a solution of 18 in CH$_2$Cl$_2$. The absolute configuration of derivative 18 was determined by X-ray diffraction analysis (Figure 15). The result shows that the $R$-configuration of the alcohol was generated by $R,R$-Ru-catalyzed asymmetric transfer hydrogenation, which is in agreement with the general rule for ATH catalyzed by Noyori’s complex. The quaternary stereogenic carbon center with the fluorine atom is assigned the $S$-configuration.

A linear chain fluorinated $\beta$-hydroxy ester was transformed to the corresponding derivatives 20 and 21 (Scheme 51). However, the attempts to grown single crystals failed.

Scheme 51. Preparation of two derivatives of a linear chain $\alpha$-fluoro-$\beta$-hydroxy ester.

1.3.8 Conformations of the $\alpha$-Fluoro-$\beta$-hydroxy Esters or Their Derivatives in the Solid State

**Literature Work:**

Due to the electronic (gauche) effect of the fluorine, the carbon-fluorine bond prefers the gauche conformation to the neighbouring carbon-heteroatom bond. Single crystal X-ray diffraction studies indicate that the preferred conformation for the vicinal F-C-C-F, F-C-C-N (CO), or F-C-C-O (CO) fragment is gauche preference rather than anti (Scheme 52).

Scheme 52. Torsion angles of vicinal fluorine-heteroatom-containing molecules (F-C-C-X).
The crystal structures of two diastereoisomeric difluorodicarboxylic acids A and B demonstrate a gauche conformation between the vicinal fluorine atoms as indicated by the corresponding F-C-C-F torsion angles of 49.0° and 75.2°, as illustrated in Scheme 53. The two amide groups of the dicarboxylic acid are oriented differently, anti to each other in A, but gauche in B. Through such stereoelectronic effect the carbon chain of the molecule is arranged either as a common zig-zag form A, or as a more contorted structure B.

Additional theoretical calculation, NMR or IR investigation, and Langmuir isotherms analysis demonstrate the existence of the fluorine gauche effect.

The crystal structures of α-fluoroamides indicate that fluorine induces a conformation such that it assumes with a vicinal carbonyl group (F-C-C=O) an anti-periplanar geometry, while with an NH group (F-C-C-N(H)) it prefers a syn-planar orientation. The torsion angles of α-fluoroamides shown in Scheme 54 reveal that the α-fluoroamide moiety is planar or distorted planar as a result of the fluorine gauche effect.

**Experimental Results**

The crystal structures of α-fluoro-β-hydroxy amide or ester, or their derivatives, as determined in this work, reveal that the conformation of the fluorinated compounds is not always in agreement with published work. The X-ray diffraction analysis of our compounds with quaternary carbon-fluorine centers show different structural features, providing new complemental information for the understanding of the conformational properties of fluorinated compounds.
Conformations of an α-Fluoro-β-hydroxy Ester and a Derivative

Phenyl 2-fluoro-3-hydroxy-2-methylpentanoate (P3) was synthesized by asymmetric fluorination of β-keto ester in the presence of \( R,R\)-Ti, and subsequent asymmetric transfer hydrogenation in the presence of \( S,S\)-Ru (Scheme 55).

![Scheme 55. Synthesis of a chiral α-fluoro-β-hydroxy ester P3.](image)

A single diastereoisomer P3 was obtained by recrystallization with >99% ee, as shown by chiral HPLC. A single crystal was obtained by diffusion of hexane into a solution of high concentration in TBME. X-ray diffraction analysis of the compound shows that the preferred conformation of the F-C-C-O(H) fragment is gauche (Figure 16, torsion angle F-C-C-O(H) is -62.1°). However, the X-ray structure indicates that the α-fluoroester adopts a syn-planar arrangement at the C-F and the C=O group, with the F-C-C=O torsion angle of 20.6°. Additionally, an anti-periplanar orientation of the C-F bond and the C-O(Ph) is found with the F-C-C-O(Ph) torsion angle of -162.1°. The conformation of an α-fluoroester is different from that of α-fluoroamide because the energy difference between the cis and trans conformation...
of an α-fluoroester is smaller (0.8-2.0 kcal mol\(^{-1}\)) than the corresponding energy difference for a fluoroamide (~7.0 kcal mol\(^{-1}\)).

The derivative 18 shown in Scheme 50 and Figure 15 displays a F-C-C-O(R) torsion angle of 62.2°, demonstrating a gauche preference between the C-F bond and the vicinal C-O bond. However, the conformation of the F-C-C=O or F-C-C(O)-O is determined by the cyclic nature of the lacton moiety and is of no relevance when discussing fluorine stereoelectronic effects.

### Conformations of an α-Fluoro-β-hydroxy Amide and a Derivative

The asymmetric reduction of a racemic mixture of α-fluoro-β-keto amide S10 in the presence of a Ru catalyst afforded the corresponding alcohol P10 with 2:1 diastereoselectivity was followed by the separation of the diastereoisomers by chromatography. An enantiomerically pure sample of P10 was obtained by recrystallization (Scheme 56, > 99% ee). Crystals for an X-ray diffraction study were obtained by diffusion of hexane into a solution of P10 in dichloromethane at 4 °C.

![Scheme 56. Preparation of an α-fluoro-β-hydroxy amide P10.](image)

**Scheme 56. Preparation of an α-fluoro-β-hydroxy amide P10.**

![Figure 17. X-ray structure of an α-fluoro-β-hydroxy amide P10.](image)

**Figure 17. X-ray structure of an α-fluoro-β-hydroxy amide P10. Selected bond length (Å): C4-F1 1.411. Selected torsion angles (°): F1-C3-C2-O1 (H) 166.4, F1-C3-C4=O2 -49.1, F1-C3-C4-N1 132.1.**

The crystal structure (Figure 17) shows that the C-F bond adopts an anti conformation rather than a gauche orientation with respect to the C-O(H) bond. The amide moiety displays a gauche interaction between the C-F bond and the C=O bond, while the C-F bond shows an anti orientation with respect to the C-N bond. Thus, the spacial arrangement of P10 in the solid state is not influenced by fluorine as one would expect, presumably because the cyclic nature of the molecule. The two rings in the molecule are nearly perfectly coplanar, which
somehow overwhelms the fluorine effect. Another unusual observation concerns the proton of hydroxyl group, which is not involved in any intramolecular hydrogen bonds.

On the other hand, the crystal structure of the derivative 17 discussed above shows the influence of fluorine on the conformation of the molecule in the solid state. The *gauche* preference of the C-F bond with the C-O(R) bond are clearly supported by the structure revealing a torsion angle of 65.1° (F-C-C-O(R)). Moreover, the *anti*-periplanar orientation of the C-F and the C=O bonds or the *syn*-planar geometry of the C-F and the C-N bonds are excluded, again because of the cyclic nature of the molecule. The orientation of the lactam ring and the phenyl ring is almost coplanar, and this plane is nearly perpendicular to the C-F bond.

### 1.4 Summary and Conclusion

In summary, a series of chiral and racemic alkyl/alkyl α-fluoro-β-keto esters and amides have been prepared via electrophilic fluorination of β-keto esters and amides. The racemic fluorinated compounds have been converted to fluorinated β-hydroxy compounds via asymmetric transfer hydrogenation catalyzed by the [(η⁶-arene)Ru(TsDPEN)] system with good yields and enantioselectivities (yields up to 95%, ee up to >99%).

The absolute configurations of the two stereogenic chiral centers of a fluorinated lactam have been determined by X-ray diffraction studies as shown in Scheme 57. The S₅S-Ti-catalyzed fluorination leads to the *R*-configuration as expected, while the S₅S-Ru-catalyzed asymmetric transfer hydrogenation of ketones generates the alcohol with *S*-configuration as described by Noyori.

![Scheme 57. A derivative 17 used for the determination of the absolute configuration.](image)

Four some cases the four enantiomerically pure fluorinated β-hydroxy esters and amides have been obtained via ATH of the corresponding racemic fluorinated compounds catalyzed by the enantiomeric Ru-complex followed by chromatography of the corresponding diastereoisomers.

In this work, conformational studies have been carried out upon the X-ray crystallographic studies of a fluorinated β-hydroxy ester or amide and their derivatives. They reveal that the carbon-fluorine bond usually prefers the *gauche* orientation with respect to the neighbouring...
1.3. Synthesis of α-Fluoro-β-hydroxy Compounds

carbon-oxygen bond because of the fluorine electronic effect. Moreover, an unexpected anti orientation was observed between the C-F and C-O(H) bonds of amide P10 and the two rings in the molecule are nearly coplanar.

1.5 References

1.5. References


1.5. Synthesis of α-Fluoro-β-hydroxy Compounds


1.5. References

1.5. Synthesis of α-Fluoro-β-hydroxy Compounds


2 Dicationic Ni Complex-Catalyzed Enantioselective 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinilnitriles

2.1 Introduction

2.1.1 General Concepts

Conjugate addition of carbon nucleophiles to electron-deficient alkenes is an important step in carbon-carbon bond-forming reactions. Stabilized carbanions, prepared by deprotonation of malonates or β-carbonyl compounds were used for this purpose. This reaction, called as “Michael addition”, has experienced extensive developments from diastereoselective, enantioselective, to catalytic enantioselective synthesis. Metal-catalyzed asymmetric Michael additions are particularly noteworthy, and organocatalyzed Michael additions have recently gained big achievements.

β-Substituted carbonyl compounds and strong nucleophilic species such as organometallic reagents belong to the class of Michael donors whereas Michael acceptors are electron-deficient alkenes like α,β-unsaturated carbonyl compounds, nitroolefins, vinilnitriles, vinylphosphates, and vinylsulfones. In comparison to other acceptors vinilnitriles have different electronic properties and their behaviors will be discussed in a later section (2.1.3). We classify all the Michael acceptors except vinilnitriles as normal acceptors. To date, the most successful asymmetric carbon-carbon bond formation are metal-catalyzed enantioselective conjugate additions to α,β-unsaturated carbonyl compounds and nitroolefins (normal acceptors). Asymmetric conjugate addition to vinylphosphates and vinylsulfones has drawn much less attention, reports on enantioselective 1,4-addition to vinilnitriles are rare, and, finally, catalytic asymmetric conjugate addition to alkenenitriles is unexplored. In the following sections, we will be focusing on the metal-catalyzed enantioselective Michael addition to the normal acceptors, as it has been done over the last few years, and highlighting the 1,4-addition reaction to vinilnitriles.

2.1.2 Michael Addition to Normal Acceptors

The appropriate combination of metal and chiral ligand yields significantly high degree of enantioselectivity and generality in asymmetric conjugate addition. We classify the following discussion in accordance to the different metal complexes.

2.1.2.1 Copper-Catalyzed Michael Addition

Chiral copper complexes obtained from chiral ligands such as phosphoramidites, phosphates, phosphines, oxazolines, and diamines are widely employed as catalysts in the
enantioselective conjugate addition reactions of organozinc, organomagnesium, and organoaluminum reagents.

Organozinc compounds represent ideal reagents due to their low reactivities towards the substrate, and, moreover, they allow the introduction of functional group to the addition product. Organomagnesium and organoaluminum are widely used in organic synthesis because of their commercial availability and easy preparation, and, moreover, they are challenging reagents towards Michael addition due to their high reactivity.

Feringa and co-workers reported highly enantioselective copper-phosphoramidite-catalyzed conjugate addition of organozinc compounds to enones (Scheme 1). They suggested a mechanism which involves transfer of an alkyl fragment from the organozinc reagent to the copper complex, followed by \( \pi \)-complexation of the resulting copper alkyl species to the double bond of e.g. cyclohexenone, and of the alkylzinc ion to the enone carbonyl (Scheme 2).^8a

![Scheme 1](image)

Scheme 1. Copper-catalyzed asymmetric conjugate addition of organozinc reagents.

![Scheme 2](image)

Scheme 2. A proposed mechanism for the Cu-catalyzed 1,4-addition of organozinc reagent to cyclohexenone.

Finally, alkyl transfer to the \( \beta \)-position of the enone takes place to generate alkylzinc enolates, which is protonated to yield cyclohexanone. Using phosphoramidite or biphenol-based phosphoramidite ligands, Alexakis et al. obtained enantioselectivity up to 96% ee in the addition of diethylzinc reagent to enones or nitroolefins.
Employing Josiphos-type ligands, Feringa and co-workers reported the Cu-catalyzed highly enantioselective 1,4-addition of organomagnesium reagents to cyclic enones,\textsuperscript{10a} acyclic enones,\textsuperscript{10b} \( \alpha,\beta \)-unsaturated esters,\textsuperscript{10c} and \( \alpha,\beta \)-unsaturated thioesters\textsuperscript{10d} (Scheme 3). The versatility of the \( \beta \)-methyl-substituted thioester was further demonstrated in the asymmetric total synthesis of (-)-lardolure\textsuperscript{10d} The mechanism of conjugate addition of Grignard reagents was explored through kinetic, spectroscopic, and electrochemical analysis.\textsuperscript{10e}

![Scheme 3. Cu-catalyzed enantioselective conjugate addition of Grignard reagents](image)

In addition to the chiral phosphine ligands, chiral N,P-, and O,P- ligands have proven to be effective for the enantioselective Cu-catalyzed conjugate addition of organozinc, organomagnesium reagents, or acetylene to various Michael acceptors, such as \( \beta \)-unsaturated ketones, or esters (Scheme 4).\textsuperscript{11}

![Scheme 4. Chiral N,P- or O,P-ligands in the Cu-catalyzed conjugate addition reaction](image)

Phosphine-free ligands also play an important role in the Cu-catalyzed conjugate addition. N,S-, O,N-, or O,S-type ligands have been recently synthesized and investigated in the highly enantioselective conjugate addition of \( \text{Et}_2\text{Zn} \) or \( \text{Ph}_2\text{Zn} \) to acyclic and cyclic enones (Scheme 5).\textsuperscript{12}
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

The conjugate addition of cyclic 1,3-dicarbonyl compounds or enamines to \( \beta,\gamma \)-unsaturated \( \alpha \)-keto esters copper-bis(oxazoline) catalyzed complexes was presented by Jørgensen and co-workers (Scheme 6).\(^{13c}\)

\[
\text{Cu(OTf)}_2, L \quad R^1 \quad R^2 \\
XH \\
\text{X} = O, NR
\]

\[
+ \quad \text{up to 98% ee}
\]

Scheme 6. Cu-bis(oxazoline) catalyzed enantioselective conjugate addition.

Asymmetric conjugate addition (i.e. Friedel-Crafts alkylation) of electron-rich aryl group to \( \alpha,\beta \)-unsaturated esters\(^{13a,b}\) or \( \beta,\gamma \)-unsaturated esters\(^{14}\) promoted by Cu-oxazoline or Cu-aza(bisoxazoline)\(^{15}\) complexes was described by Jørgensen, Tang, and Reiser, respectively (Scheme 7). A Cu-oxazoline catalyst (Scheme 7) was utilized in the asymmetric Mukaiyama-Michael addition reaction of alkylidene malonates and enolsilanes by Evans to afford adducts with moderate enantioselectivities and, in the case of large substituent, products with higher enantioselectivities (ee > 90%).\(^{16}\)
2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinylnitriles

![Chemical structures](image)

Scheme 7. Chiral oxazoline ligands in the Cu-catalyzed conjugate addition.

* N-Heterocyclic carbenes (NHCs) ligands were also successfully used in the Cu-catalyzed conjugate addition of organozinc reagents,\(^{17a-c}\) organoaluminium reagents,\(^{17c}\) and Grignard reagents\(^{17c}\) to enones. A stereogenic quaternary carbon center was constructed by the addition of Grignard reagents to a trisubstituted enone (Scheme 8).\(^{17c}\) The copper catalyst was generated *in situ* by deprotonating the corresponding imidazolidinium NHC salt (ImH\(^+\)) with butyllithium or even with the Grignard reagent itself in the presence of copper (II) triflate.

![Chemical structures](image)

Scheme 8. Cu-NHC catalyzed conjugate addition

### 2.1.2.2 Rhodium-Catalyzed Enantioselective Conjugate Addition

The Cu-catalyzed enantioselective conjugate addition discussed above mostly introduces alkyl groups to a Michael acceptor, while the highly enantioselective transfer of aryl- or alkenyl-groups occurs via Rh-catalyzed enantioselective conjugate addition of organoboronic acids to various \(\alpha,\beta\)-unsaturated compounds in the presence of BINAP or \(\text{H}_2\text{BINAP}\), as developed by Hayashi et al.\(^{3d,e,18}\)

Formation of a quaternary carbon center on substituted maleimides, catalyzed by the Rh-BINAP system, was reported by Hayashi through 1,4-addition (Scheme 9).\(^{19a}\) It was proposed that transmetalation of an aryl group to rhodium followed by the insertion of enone into the aryl-rhodium bond thereby generating a rhodium enolate (Scheme 10).\(^{20,3f}\) The rhodium enolate thus formed undergoes hydrolysis giving rise to 1,4-addition product and a hydroxorhodium species. The three intermediates (phenylrhodium, \(\text{oxa-}\pi\text{-allyl}\)rhodium, and
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

Hydroxorhodium species) have been observed in NMR spectroscopic studies. Organosilane reagents as Michael donors and vinylphosphates, or nitroolefins as Michael acceptors have also been used in the Rh-BINAP-catalyzed 1,4-addition reaction.

\[
\begin{align*}
&\text{[RhCl(C_2H_4)_2], L,} \\
&\text{PhB(OH)_2, dioxane/H_2O 10/1, KOH,} \\
&\text{0.5 eq., 50°C, 3 h} \\
&\text{upto 98% ee}
\end{align*}
\]

Scheme 9. Enantioselective Rh-catalyzed 1,4-addition reaction.

Feringa and co-workers used a combination of Rh and chiral monodentate phosphoramidite ligands (Scheme 11) as catalyst in the conjugate addition of boronic acids or potassium organotrifluoroborate to enones or nitroolefins, providing highly enantioenriched adducts. The use of phosphanes, phosphonites or phosphites (Scheme 11) as ligands in the Rh-catalyzed conjugate addition of arylboronic acids to \(\alpha,\beta\)-unsaturated compounds afforded adducts with high enantioselectivity.
2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinylnitriles

Scheme 11. P-containing ligands used in Rh-catalyzed conjugate addition.

*N*-heterocyclic carbenes (NHCs) (Scheme 12)\(^{26}\) and camphor-based diene type ligands (Scheme 13)\(^{19a,27}\) have been found to be versatile ligands in the Rh-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic and acyclic enones and \(\alpha,\beta\)-unsaturated esters.

Scheme 12. Carbenes (NHCs) ligands in Rh-catalyzed conjugate addition.

Scheme 13. P-free diene ligands in Rh-catalyzed conjugate addition.
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylethers

2.1.2.3 Other Metals-Catalyzed Enantioselective 1,4-Addition Reaction

Other chiral metal complexes (M = La, Ru, Pd, Ru, Ni, Sc, etc) have been efficiently employed as catalysts in an enantioselective Michael addition of β-keto esters or their analogues to a range of structurally diverse electron-deficient olefins. Shibasaki’s La-NR-linked-BINOL complex promotes a variety of enantioselective conjugate addition to α,β-unsaturated ketones, α,β-unsaturated acid imidazolides, and α,β-unsaturated N-acylpyrroles. In the presence of Sodeoka’s palladium-BINAP catalyst, asymmetric conjugate addition of 1,3-dicarbonyl compounds to cyclic or acyclic enones affords products with high enantioselectivities.

The M/NH bifunctional effect of Noyori-Ikariya’s ruthenium-amido catalyst bearing sufficient Bronsted basicity was found to be crucial to the catalytic C-C bond formation through conjugate addition. Jacobsen’s aluminum-salen complexes are effective in asymmetric conjugate addition of various nucleophiles to α,β-unsaturated-ketones, and imides. Evans and co-workers recently reported Ni(II)- or Sc(III)-catalyzed asymmetric conjugate addition of a range of nucleophiles to different Michael acceptors (α,β-unsaturated ketones, α,β-unsaturated 2-acyl imidazoles, α,β-unsaturated N-acylthiazolidinethiones, α,β-unsaturated phosphates, and nitroolefins).

![Scheme 14. Some other metal-complexes used in asymmetric conjugate addition.](image)

Moreover, further contributions from asymmetric conjugate addition catalyzed with other metals such as Zn, Ni, and Ag have to be mentioned in order to complete this overview. Finally, based on the metal-catalyzed enantioselective conjugate addition, a series of asymmetric tandem transformations have been recently developed and efficiently applied in the construction of complex multifunctional and multistereogenic molecules in one-pot processes.
2.1.3 Michael Addition to Vinylcitriles

Asymmetric conjugate addition reactions have been extensively investigated and applied for the enantioselective C-C bond formation in organic synthesis. Vinylcitriles are inert to nucleophiles in comparison to other Michael acceptors and rarely undergo asymmetric conjugate addition because of their peculiar electronic properties. The presence of strong electron-withdrawing nitrile group polarizes the alkenenitrile such that its π-system is less delocalized. In other words, the nitrile group exerts a greater electron-withdrawing effect on the α-carbon than on the β-carbon leading the nucleophilic attack to the nitrile group, i.e., 1,2-addition reaction. The key requirement for conjugate addition to vinylcitriles is the employment of highly nucleophilic reagent that does not generate 1,2-addition product.

The substitution of the α,β-unsaturated nitriles has a crucial effect on the reactivity of the vinylcitrile. A general reactivity order for substituted acrylonitriles is illustrated in Scheme 15.

Scheme 15. A general reactivity order for substituted acrylonitriles

Acrylonitrile is significantly more active than any other unsaturated nitriles, which is analogous to the related activated alkene. α- or β-Substituents dramatically retard the conjugate addition to alkenenitriles, presumably due to the increasing steric hindrance and the diminishing electropositive character of the β-carbon.

Conjugate addition of various enolates, metal-reagents, enamines to alkenenitriles has been reviewed in detail. We discuss the very recent literature work that has led to excellent results and highlight asymmetric conjugate addition to vinylcitriles.

2.1.3.1 Conjugate Addition of Organometallic Reagents to Vinylcitriles

Conjugate addition of Grignard reagents to acyclic and cyclic γ-hydroxy-α,β-unsaturated nitriles was efficiently promoted by the chelation of the hydroxy group of alkenenitrile and the Grignard reagent affording the desired 1,4-conjugate adducts in good yields.

A chelating model was proposed by Fleming and co-workers for the above discussed conjugate addition. Deprotonation of the hydroxy group at -78 °C generates the halomagnesium alkoxide A, which rapidly engages in a halogen-alkyl exchange with excess R'MgCl. The resulting alkylmagnesium alkoxide B initiates a smooth conjugate addition generating the conjugate adduct (Scheme 17).
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

\[
\text{alkenenitriles} \xrightarrow{\text{t-BuMgCl, 1 eq}} \text{1,4-adducts}
\]

\[\text{HO} - \text{CN} \xrightarrow{\text{RMeGIX, 1.1-1.5 eq}} \text{Me, Bu, Ph, cyclopentyl, CH2=CH, Ph etc.} \]

![Scheme 16. Conjugate addition of Grignard reagents to alkenenitriles.](image)

Grignard reagents undergo conjugate addition to alkenenitriles, whereas other organometallic reagents of Cr, Mn, Co, Ni, Cu, and Zn mostly lead to a radical-type addition reaction. For example, Zn, or Zn-Cu-promoted conjugate addition of functionalized alkyl iodides to disubstituted alkenenitriles in water gives the corresponding functional nitriles in good yields (Scheme 18).

\[\text{R} - \text{CN} \xrightarrow{\text{Zn-Cu, H2O}} \text{64-82% yield}
\]

![Scheme 18. Zn-Cu-Promoted conjugated addition to alkenenitriles.](image)

2.1.3.2 Conjugate Addition of Stabilized Carbanions or Enamines to Vinylnitriles

The addition of stabilized carbanions or enamines to \(\alpha,\beta\)-unsaturated nitriles was performed in a buffered solution. Deprotonation of the nucleophile (mostly carbonyl compounds) by base generates the corresponding anion having some degree of nucleophilicity.
The general order of increasing nucleophilicity of the anions towards conjugate addition is: diones < ketoesters < malononitrile < malonates < nitromethane, followed by metalated ketones, esters, nitriles, and nitroalkanes.\(^{40}\) Asymmetric conjugate addition of carbanions or enamines to alkenenitriles will be reported in the following section.

### 2.1.3.3 Diastereo-, Enantioselective Conjugate Addition to Vinylnitriles

Diastereo-, enantioselective conjugate additions to \(\alpha,\beta\)-unsaturated nitriles have been rarely explored, but there are few examples where the induction of chirality are based on chiral substrates, substrates’ chiral auxiliary groups, or enamines derived from chiral amines and ketones. An interesting application of diastereoselective conjugate addition to acrylonitrile is the synthesis of the pseudoguianolide (\(+\))-confertin by converting the corresponding adduct in a multi-step sequence (Scheme 19).\(^{41}\)

![Scheme 19. Conjugate addition of chiral ketone to acrylonitrile under basic condition.](image)

Construction of a quaternary carbon center was realized via asymmetric intramolecular cyclization of an enantiomerically pure alkenenitrile. The anionic cyclization was completed through metal-halogen exchange with the desired diastereoselection, wheras the undesired isomer was obtained through radical cyclization (Scheme 20).\(^{42}\)

![Scheme 20. Asymmetric conjugate addition of lithium reagent to alkenenitrile.](image)

Evans and co-workers described that diastereoselective conjugate addition of a titanium enolate derived from a chiral \(N\)-propionyloxazoline to acrylonitrile gave an adduct with high diastereoselectivity (\(\text{dr} > 200:1\), Scheme 21).\(^{43}\)

![Scheme 21. A diastereoselective conjugate addition to acrylonitrile.](image)
Using resin-supported Evans’ chiral auxiliary, conjugate addition to acrylonitrile proceeded smoothly affording the 1,4-adduct with good enantioselectivity (Scheme 22).\textsuperscript{44} Prior to addition of acrylonitrile, enolization of propionyl group in the resin-supported oxazolidinone was carried out in the presence of TiCl$_3$(i-OPr) and DIEPA. The enantiomeric excess was determined by two further conversions of the adduct to the amide, whose diastereomeric ratio was determined by $^1$H NMR to be 89:11.

![Scheme 22. Solid state conjugate addition using Evans’ oxazolidinone chiral auxiliary.](image)

Similarly, chiral enamines derived from chiral amines are employed in asymmetric conjugate addition. Conjugate addition of a proline-derived enamine \textsuperscript{45} or a phenylethylamine-derived enamine \textsuperscript{46} to acrylonitrile, respectively, presented moderate enantioselectivity (Scheme 23).

![Scheme 23. Enantioselectivities in 1,4-addition of chiral enamines to acrylonitrile.](image)

Asymmetric conjugate addition of chiral enamines to acrylonitrile can be enhanced in the presence of the Lewis acid MgCl$_2$ affording the corresponding adducts in high enantioselectivity (95% ee).\textsuperscript{47} A key chiral nitrile was synthesized with 90% ee, and converted to a trioxane, an analogue of the antimalarial agent artemisinine, in a multistep sequence (Scheme 24). The configuration of the two isomers was confirmed by X-ray analysis.
2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinyl nitriles

\[
\text{[Image showing a chemical reaction]} \quad \text{MgCl}_2, \text{C}_6\text{H}_6, \text{reflux} \quad 48\% \text{ yield} \quad 90\% \text{ ee}
\]

\[ R^1 = \text{OMe}, R = \text{H}, 25\% \text{ yield}, 85\% \text{ ee} \]
\[ R^1 = \text{H}, R = \text{OMe}, 15\% \text{ yield}, 85\% \text{ ee} \]

Scheme 24. MgCl₂-Promoted conjugate addition of chiral enamine to acrylonitrile.

Naturally, alkenenitriles with an additional electron-withdrawing group easily undergo conjugate addition due to high reactivity of the doubly activated olefin. However, asymmetric conjugate addition of alkenenitriles with additional electron-withdrawing groups has rarely been explored. Recently, a chiral enamine, derived from phenylethylamine and a ketone, reacted with 2-acetoxyacrylonitrile providing a multifunctional nitrile in good yield with excellent diastereoselectivity and enantioselectivity (72% yield, dr > 9:1, >95% ee) (Scheme 25).

\[
\text{[Image showing a chemical reaction]} \quad \text{72\% overall yield} \quad \text{dr > 9:1, >95\% ee}
\]

Scheme 25. Diastereoselective conjugate addition of chiral enamine to 2-acetoxyacrylonitrile.

Using cinchona alkaloids as dual-function chiral catalysts, conjugate additions of various Michael donors to 2-chloroacrylonitrile were achieved, in the construction of 1,3-tertiary-quaternary stereocenters in good to excellent diastereo- and enantioselectivities (dr up to 25:1, ee up to 99%, Scheme 26). The contribution has opened a new prospect of enantioselective conjugate addition via organocatalysis although the vinyl nitrile contains an activating functional group.

\[
\text{[Image showing a chemical reaction]} \quad \text{71-95\% yield} \quad \text{dr = 5:1 to 25:1 up to 99\% ee}
\]

Scheme 26. Cinchona alkaloid-catalyzed conjugate addition to 2-chloroacrylonitrile.
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

In addition, a few radical-type asymmetric conjugate additions of chiral substrate to alkenenitriles are important complement to the generation of enantiomerically enriched nitrile compounds.\(^5^0\)

In summary, catalytic asymmetric conjugate addition of various nucleophiles, including stabilized carbanions, enamines, and organometallic reagents, to a variety of \(\alpha,\beta\)-unsaturated carbonyl compounds, vinylphosphates, and vinylsufones have been achieved in a highly enantioselective manner. However, enantioselective and catalytic asymmetric conjugate additions to alkenenitriles are still demanding and challenging tasks.

2.2 Results and Discussion

Conjugate addition to vinylnitriles is a generally useful method for the synthesis of compounds containing a nitrile group and has been extensively investigated in the past decades. However, as mentioned above, compared to \(\alpha,\beta\)-unsaturated carbonyl compounds, vinylnitriles have rarely been involved in catalytic asymmetric conjugate addition mainly due to its electronic and geometric property.

Structurally characterized tridentate \(\text{Pigiphos}\) ligand and its metal (Ni, Pd, Ru, Rh, etc.) complexes have been reported by our group.\(^5^1\) These metal complexes have been used in asymmetric catalysis and Ni(II)-\(\text{Pigiphos}\) complexes are most effective catalysts in enantioselective hydroamination\(^5^2\) and hydrophosphination of vinylnitriles.\(^5^3\) The vinylnitrile is activated by the coordination of the nitrogen atom of the nitrile group to a dicationic Ni-complex and is followed by the 1,4-nucleophilic addition of primary and secondary amines or secondary phosphines to yield chiral amines or phosphines with high ee’s. Encouraged by these results, we have been focusing on the further investigation of the dicationic complexes in the catalytic asymmetric C-C bond-forming reaction between vinylnitriles and carbon nucleophiles.

2.2.1 Synthesis of Ligands and Ni (II) Complexes

\(\text{Pigiphos}\)-type ligands (L\(_1\)-L\(_4\)) were easily synthesized from Ugi-amine according to the methods reported by our group (Scheme 27).\(^5^1,\,5^4\) The addition of \(R_2\text{PCl}\) to lithiated Ugi-amine gives the corresponding (\(R\)-(S))-PPFA-type intermediate. Treatment with \(\text{CyPH}_2\) or \(\text{PhPH}_2\) in the presence of \(\text{CF}_3\text{COOH}\) in acetic acid affords a variety of \(\text{Pigiphos}\)-type ligands (L\(_1\)-L\(_4\)) in moderate to good yield (49-77%).

The dicationic nickel-\(\text{Pigiphos}\) complexes (Ni\(_1\)-Ni\(_6\)) were prepared as shown in Scheme 28.\(^5^1,\,5^4\) The catalyst precursor [Ni(H\(_2\text{O}\))\(_6\)](X)\(_2\) (X = BF\(_4\), ClO\(_4\), or BPh\(_4\)) and \(\text{Pigiphos}\)-type ligands (L\(_1\)-L\(_4\)) were reacted in acetonitrile, THF, methacrylonitrile, etc., to give a deep purple or brown solution of [Ni(L\(_a\))(sol)](X)\(_2\). Purification by filtration and evaporation of the
filtrate under high vacuum afforded the Ni(II) complexes as deep purple powder (Ni_A, Ni_B, Ni_D, Ni_F, and Ni_G) or yellow powder (Ni_C and Ni_E).

Scheme 27. Synthesis of Pigiphos-type ligands

\[
\text{Fe} \quad \text{P} \quad \text{Fe} \quad \text{P} \\
\text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \\
\text{L}_4, 70\% \\
\]

Scheme 28. Synthesis of dicationic nickel(II) complexes

X-ray quality crystals of two dicationic Ni(II) complexes were obtained from slow diffusion of hexane into a highly concentrated dichloromethane solution of the corresponding complex. The solid state structures were determined by X-ray crystallography. The structures of Ni_A and Ni_B display the dicationic fragment \([\text{Ni}(\text{Pigiphos})]^2^+\), two BF_4^- counterions, and a coordinated nitrile molecule (Ni_A with acetonitrile and Ni_B with methacrylonitrile), with an additional dichloromethane molecule in the unit cell. The dicationic Ni_A and Ni_B are illustrated in Figure 1 and Figure 2, respectively. Selected bond distances and angles are found in Table 1 and Table 2.
In asymmetric unit of crystals of NiA, one molecule of the complex and one molecule of solvent CH₂Cl₂ are present. The nickel center is coordinated with three phosphorus atoms and the acetonitrile in a distorted square-planar geometry. The bond lengths Ni-P (Ph) and Ni-P (Cy) are 2.2421, 2.2504, and 2.1843 Å, respectively. The bond length Ni-N is 1.898 Å. The Ni atom is located 0.336 Å from the plane defined by the three phosphorus atoms. The nitrogen (N1), carbon (C25), carbon (C26) atoms are further displaced from this plane (in the same direction) by 1.510 Å, 1.824 Å, and 2.726 Å, respectively. This distortion is also demonstrated by the angles formed by the Ni center and its sets of trans ligands, i.e., P1-Ni1-P1A (160.34 °), and P2-Ni1-N1 (163.40 °), which are significantly lower than 180°.
Similarly, the asymmetric unit of crystals of \( \text{Ni}_B \) contains one molecule of the complex and one molecule of solvent \( \text{CH}_2\text{Cl}_2 \). The bonds lengths \( \text{Ni}-\text{P} \text{ (Ph)} \) and \( \text{Ni}-\text{P} \text{ (Cy)} \) are 2.2391, 2.2524, and 2.1785 Å, respectively, whereas the \( \text{Ni}-\text{N} \) distance is 1.877 Å. The geometry of \( \text{Ni}_B \) is very similar to that of \( \text{Ni}_A \) (Figure 2). A distorted square-planar geometry is found around \( \text{Ni} \). The distance from \( \text{Ni} \) to the plane defined by the three phosphorus atoms is 0.311 Å. The nitrogen (N1), carbon (C55), and carbon (C56) atoms are displaced from the plane in the same direction by 1.055 Å, 1.754 Å, and 2.685 Å, respectively. This distortion, again, is demonstrated by the angles formed by the \( \text{Ni} \) center and its sets of \textit{trans} ligands, i.e., P1-Ni1-P3 (161.26°), and P2-Ni1-N1 (164.83°), which significantly deviate from 180°.
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

Table 1. Selected bond lengths (Å) for \([\text{Ni(P}g_{	ext{i}}\text{gphos})(\text{NCMe})](\text{BF}_4)_2 (\text{Ni}_A)\) and \([\text{Ni(P}g_{	ext{i}}\text{gphos})(\text{NCMeC}=\text{CH}_2)](\text{BF}_4)_2 (\text{Ni}_B)\).

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<tr>
<th>Bond length (Å)</th>
<th>(\text{Ni}_A)</th>
<th>(\text{Ni}_B)</th>
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<tr>
<td>(\text{Ni}(1)-\text{N}(1))</td>
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<td>1.877(3)</td>
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<tr>
<td>(\text{Ni}(1)-\text{P}(1))</td>
<td>2.242(8)</td>
<td>2.239(9)</td>
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<tr>
<td>(\text{Ni}(1)-\text{P}(2))</td>
<td>2.184(7)</td>
<td>2.178(9)</td>
</tr>
<tr>
<td>(\text{Ni}(1)-\text{P}(1A)) or (\text{P}(3) (\text{Ni}_B))</td>
<td>2.250(4)</td>
<td>2.252(4)</td>
</tr>
<tr>
<td>(\text{N}(1)-\text{C}(25))</td>
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<tr>
<td>(\text{C}(56)-\text{C}(58))</td>
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</table>

Table 2. Selected bond angles (deg) for \([\text{Ni(P}g_{	ext{i}}\text{gphos})(\text{NCMe})](\text{BF}_4)_2 (\text{Ni}_A)\) and \([\text{Ni(P}g_{	ext{i}}\text{gphos})(\text{NCMeC}=\text{CH}_2)](\text{BF}_4)_2 (\text{Ni}_B)\).

<table>
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<th>Bond angle (°)</th>
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<th>(\text{Ni}_B)</th>
</tr>
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<tbody>
<tr>
<td>(\text{N}(1)-\text{Ni}(1)-\text{P}(2))</td>
<td>163.40(10)</td>
<td>164.83(13)</td>
</tr>
<tr>
<td>(\text{N}(1)-\text{Ni}(1)-\text{P}(1))</td>
<td>91.29(8)</td>
<td>90.25(9)</td>
</tr>
<tr>
<td>(\text{N}(1)-\text{Ni}(1)-\text{P}(1A)) or (\text{P}(3) (\text{Ni}_B))</td>
<td>87.54(8)</td>
<td>87.03(9)</td>
</tr>
<tr>
<td>(\text{P}(2)-\text{Ni}(1)-\text{P}(1))</td>
<td>90.89(3)</td>
<td>91.39(3)</td>
</tr>
<tr>
<td>(\text{P}(2)-\text{Ni}(1)-\text{P}(1A)) or (\text{P}(3) (\text{Ni}_B))</td>
<td>95.82(3)</td>
<td>96.07(3)</td>
</tr>
<tr>
<td>(\text{P}(1)-\text{Ni}(1)-\text{P}(1A)) or (\text{P}(3) (\text{Ni}_B))</td>
<td>160.34(3)</td>
<td>161.26(4)</td>
</tr>
<tr>
<td>(\text{C}(25)-\text{N}(1)-\text{Ni}(1))</td>
<td>168.1(4)</td>
<td></td>
</tr>
<tr>
<td>(\text{N}(1)-\text{C}(25)-\text{C}(26))</td>
<td>179.0(6)</td>
<td></td>
</tr>
<tr>
<td>(\text{C}(55)-\text{N}(1)-\text{Ni}(1))</td>
<td></td>
<td>164.7(5)</td>
</tr>
<tr>
<td>(\text{N}(1)-\text{C}(55)-\text{C}(56))</td>
<td></td>
<td>177.5(6)</td>
</tr>
</tbody>
</table>

2.2.2 1,4-Addition of 1,3-Carbonyl Compounds to Methacrylonitrile

2.2.2.1 1,4-Addition of β-Keto Esters to Methacrylonitrile

With the Ni(II)-complexes as nitrile activators in hand, first attempts towards the 1,4-addition of the 1,3-dicarbonyl \(S_{23}\) to methacrylonitrile were carried out under the same condition as in hydroamination and hydrophosphination previously developed in our group.\textsuperscript{52,53} The product \(P_{23}\) is formed as a mixture of two diastereoisomers. However, in the presence of Ni(II) complex \(\text{Ni}_A\), the addition of the β-keto ester to methacrylonitrile did not take place (Table 3, entry 1). Compared to the nucleophilicity of nitrogen (hydroamination) or phosphine (hydrophosphination), that of carbon is much weaker. The nucleophilicity of 1,3-
dicarbonyl compounds can be enhanced through the generation of corresponding enolates. Subsequently, we purposely explored the Ni(II)-catalyzed conjugate addition in the presence of Lewis acids or bases.

Table 3. Initial attempts of Lewis acid-activator in the 1,4-addition.

<table>
<thead>
<tr>
<th>entry</th>
<th>condition</th>
<th>yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiA</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NiA, CpTiCl₃</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NiA, R,R-Ti1, AgPF₆</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NiA, R,R-Ti2</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NiA, R,R-Ru</td>
<td>12</td>
<td>1:1</td>
<td>24, 30</td>
</tr>
<tr>
<td>6</td>
<td>R,R-Ru</td>
<td>n.d.</td>
<td>1:1</td>
<td>37, 39</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise noted, the reaction was performed using 5 mol% of catalyst and 5 mol% of additive in 1-2 mL of methacrylonitrile at room temperature over one week. \(^b\) Isolated yields by chromatography. \(^c\) Determined by \(^1\)H NMR. \(^d\) Determined by chiral HPLC. \(^e\) Not determined.

Ti(IV) complexes have been widely and successfully used in asymmetric electrophilic substitution reactions (halogenation (F, Cl, Br), hydroxylation, and sulfonylation of \(\beta\)-keto ester),\(^{55}\) indicating that they are good Lewis acids for the formation of enolate from \(\beta\)-keto esters. Initial use of CpTiCl₃ or R,R-Ti1 as co-catalyst in the 1,4-addition did not give positive results (entries 2, 3). The chlorine of the Ti(IV) complex is a stronger ligand than methacrylonitrile and might deactivate the dicationic Ni(II) complex by replacing methacrylonitrile. A dicationic titanium complex was generated by addition of 2 equiv of AgPF₆ to scavenge chlorine. However, combination of the dicationic Ni(II) and Ti(IV) did not realize the desired reaction. Even the isolated complex \([\text{Ti}(1-Np-TADDOLato)(carbonylenolato)]\)\(^{56}\) R,R-Ti2 did not work in the 1,4-addition (entry 4).

Ru-complexes of the type of Noyori’s catalyst, (R,R-Ru) have shown high activity in Michael addition of 1,3-dicarbonyl compounds to enones or nitroolefins,\(^{57}\) whereas, the
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

conjugate addition to alkenenitriles has not yet been explored specifically using the Ru-amido complex. We found that this Ru-complex as an activator towards β-keto esters, conjugate addition to methacrylonitrile in the presence of the Ni(II)-complex NiA, affords the desired product, albeit in 12% yield and with low enantioselectivities (entry 5, 24% and 30% ee). However, the control reaction indicated that the bifunctional Ru-amido complex itself catalyzes the 1,4-addition reaction with comparably low enantioselectivity (entry 6, 37%, 39% ee). The dual activation of substrates by the Ru-amido complex takes place by coordination of methacrylonitrile through its nitrogen atom and deprotonation of β-keto ester by the basic amino-ligand.57,58 The disadvantage of this Ru complex is the inefficient transfer of chirality. However, from the hint of activity of the basic amido ligand, we looked for appropriate bases for the enhancement of nucleophilicity of 1,3-dicarbonyl compounds in conjugate addition to vinylnitriles activated by our Ni(II) complexes.

Table 4. Use of bases as co-catalysts in the 1,4-addition of β-keto ester to methacrylonitrile. a

<table>
<thead>
<tr>
<th>entry</th>
<th>base b</th>
<th>yield (%) c</th>
<th>ee (%) d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hunig base</td>
<td>9</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>TMP</td>
<td>8</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>proton sponge</td>
<td>63</td>
<td>34, 32</td>
</tr>
<tr>
<td>4e</td>
<td>proton sponge</td>
<td>71</td>
<td>23, 34</td>
</tr>
<tr>
<td>5e</td>
<td>DBU (5 mol%)</td>
<td>83</td>
<td>20, 25</td>
</tr>
<tr>
<td>6</td>
<td>Sparteine</td>
<td>4</td>
<td>25, 29</td>
</tr>
</tbody>
</table>

a Unless otherwise noted, the reactions were performed using 0.25 mmol of β-keto ester, 5 mol% of [Ni(Pigiphos)THF](CIO4)_2, 10 mol% of base, in 1-2 mL of methacrylonitrile at room temperature for one week.
b Hunig base: disopropylethylamine; TMP: 2,6-di-tert-butylpyridine; Proton sponge: (N,N,N,N-tetramethyl-1,8-naphthalenediamine (or 1,8-bis(dimethylamino)naphthalene); DBU: 1,8-diazabicyclo[5.4.0]-7-ene; DABCO: 1,4-diazabicyclo[2.2.2]octane. c Isolated yields by flash chromatography. d Ee of two diastereomers (dr = 1:1, by 1H NMR and HPLC) determined by chiral HPLC. e At 50 °C, 24 h.

Promising results were obtained after screening various bases (Table 4). The hindered bases afforded trace of P23 (entries 1, 2) whereas a stronger base such as proton sponge gave a good yield (entry 3, 63%). The reaction proceeded extremely sluggishly at room temperature (around one month), whereas the reaction was completed in one day at 50 °C (entries 4, 5) with low enantioselectivity (20-34% ee). Even in the presence of the chiral base sparteine we did not observe any enhancement in the enantioselectivity (entry 6, 25% and 29% ee for the
two diastereoisomers). The diastereroselectivity was 1:1, as also observed in the following 1,4-additions of other β-keto esters, unless otherwise noted.

The conjugate addition of another α-unsubstituted β-keto ester to methacrylonitrile was attempted. The desired product P24a was isolated in 24% yield, along with the double conjugate addition product P24b in 37% isolated yield (Scheme 29).

![Scheme 29. 1,4-Addition of an α-unsubstituted β-keto ester to methacrylonitrile.](image)

All preliminary investigation of 1,4-addition of β-keto esters to methacrylonitrile gave a mixture with 1:1 diastereomeric ratio. Since no diastereoselective product formation was observed, the substrates were simplified to symmetric 1,3-dicarbonyl compounds such as diesters or diketones. Symmetric diesters (Scheme 30) showed low or no activity whereas diketones turned out to be promising nucleophiles in the conjugate addition to methacrylonitrile.

![Scheme 30. Some symmetric diesters showing no reactivity towards methacrylonitrile](image)

### 2.2.2.2 1,4-Addition of 1,3-Diketones to Methacrylonitrile

**Preliminary Results**

Preliminary results showed that diketones are suitable nucleophiles in 1,4-addition reaction of 1,3-dicarbonyl compounds to methacrylonitrile and thus they were explored in more detail as Michael donors in such conjugate additions. Initially, using 3-methyl-2,4-pentanedione (S25) as a model substrate, conjugate addition to methacrylonitrile was attempted and the results showed that the basic additive was crucial to the reaction (Table 5). The yield of the product did not increase even when the amount of the base was increased to 2 equiv. Yield and enantiomeric excess dropped dramatically when the catalyst loading was decreased to 2 mol% (entry 6, 3% yield, 4% ee). In addition, using molecular sieves as additive did not improve the selectivity and reactivity (Table 5, entry 2 vs entry 4). With these preliminary results in hand, different reaction conditions such as catalysts, ligands, bases,
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinyl Nitriles

Solvents, temperature, counterions were optimized for the conjugate addition of 1,3-diketones to methacrylonitrile.

Table 5. Preliminary attempts in the 1,4-addition of 3-methyl-2,4-pentanedione to methacrylonitrile.*

<table>
<thead>
<tr>
<th>entry</th>
<th>cat</th>
<th>Additive</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mol%</td>
<td>4Å MS</td>
<td>4</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>5 mol%</td>
<td>DBU, 4Å MS</td>
<td>77</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>DBU, 4Å MS</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>5 mol%</td>
<td>DBU, no 4Å MS</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>5 mol%</td>
<td>DBU (2 eq)</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>2 mol%</td>
<td>DBU</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Unless otherwise specified, reactions were performed using 0.5 mmol of substrate, 5 mol% of Ni, 5 mol% of basic additive (DBU) in 1-2 mL of methacrylonitrile at 50 °C for 4-5 days. b Isolated yields after flash chromatography. c Ee measured by chiral HPLC.

Screening Catalysts

A variety of catalysts containing the tridentate ligand *Pigiphos* were screened in the 1,4-addition of 3-methyl-2,4-pentanedione to methacrylonitrile (Table 6). A dicationic palladium complex proved active, however, the enantioselectivity of the conjugate addition was poor (entry 2, 84% yield, 14% ee). Other metals such as copper (I), copper (II), or silver, show no catalytic activity in the addition reaction, whereas transition metals such as ruthenium or rhodium displayed only very low activity. Dicationic Ni(II)-*Pigiphos* complexes are thereby demonstrated to be superior catalysts in the conjugate addition to methacrylonitrile.

Ligands Effects

The different *Pigiphos*-type ligands available (Scheme 27, Lₐ) were examined (Table 7). The corresponding dicationic Ni(II) complex (Niₐ) were prepared as shown in Scheme 28. The electronic and steric factors of the dicationic Ni(II) catalysts have a greater impact on the reaction rate and selectivity. It turned out that *Pigiphos* (L₁) gave highest activity and selectivity (entry 1), whereas ligand L₂ having electron-withdrawing groups showed no activity in the conjugate 1,4-addition reaction. Ligand L₃ possessing the sterically bulky
groups 1,3-dimethylphenyl connected to the phosphorus led to low enantioselectivity and $L_4$ was even less promising (entry 4).

Table 6. Examination of catalysts in the 1,4-addition of 3-methyl-2,4-pentanedione to methacrylonitrile.

<table>
<thead>
<tr>
<th>entry</th>
<th>Lewis acid</th>
<th>time (d)</th>
<th>yield (%) $^b$</th>
<th>ee (%) $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="BF$_4$">Ni(Pigiphos)(CH$_3$CN)</a>$_2$</td>
<td>5</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td><a href="BF$_4$">Pd(MeCN)$_4$</a>$_2$, Pigiphos</td>
<td>2</td>
<td>87</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$ trimer, Pigiphos</td>
<td>3</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)$_2$, Pigiphos</td>
<td>5</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>(CuOTf)$_2$C$_6$H$_6$, Pigiphos</td>
<td>5</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>AgOTf, Pigiphos</td>
<td>~5</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td><a href="BF$_4$">Ru(Pigiphos)(CH$_3$CN)$_2$</a>$_2$</td>
<td>3</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>(Rh(COD)Cl)$_2$, Pigiphos, AgPF$_6$</td>
<td>3</td>
<td>low</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise specified, reactions were performed using 0.25-0.5 mmol of substrate, 5 mol% of metal precursors, 5 mol% of Pigiphos, or 5 mol% of isolated metal complex, 5 mol% of base (DBU) in 1-2 mL of methacrylonitrile at 50 °C. $^b$ Isolated yields after flash chromatography. $^c$ Ee measured by chiral HPLC.

Table 7. Ligands effects.

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand ($L_n$)</th>
<th>reaction time</th>
<th>yield (%) $^b$</th>
<th>ee (%) $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$L_1$</td>
<td>5 d (~106 h)</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>$L_2$</td>
<td>10 d</td>
<td>0 (polymer formed)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>$L_3$</td>
<td>3 d</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>$L_4$</td>
<td>5 d</td>
<td>trace (TLC) n.d.</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise specified, reactions were performed using 0.25-0.5 mmol of substrate, 5 mol% of DBU, 5 mol% of cat [Ni($L_n$)(CH$_3$CN)](BF$_4$)$_2$ in 1-2 mL of methacrylonitrile. $^b$ Isolated yields after flash chromatography. $^c$ Ee measured by chiral HPLC.

Screening Additives I – Using Base as a Promotor

In the above discussion, it was shown that a base (DBU) accelerated the rate of the conjugate addition reaction. Subsequently, easily available bases were screened in the presence of the dicationic Ni(II)-Pigiphos complex, in the conjugate addition to methacrylonitrile and the results are summarized in Table 8.
Table 8. Screening bases in the 1,4-addition of 3-methyl-2,4-pentanedinone to methacrylonitrile.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time (d)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU</td>
<td>5</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>proton sponge</td>
<td>5</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>DABCO</td>
<td>5</td>
<td>Trace</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>Cy₂NMe</td>
<td>6</td>
<td>49</td>
<td>&lt;40</td>
</tr>
<tr>
<td>5</td>
<td>TMP</td>
<td>5</td>
<td>&lt;20</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>BSA/KOAc, 4Å MS</td>
<td>3</td>
<td>23</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>KOAc</td>
<td>11</td>
<td>24</td>
<td>61</td>
</tr>
</tbody>
</table>

Unless otherwise specified, reactions were performed using 0.25-0.5 mmol of substrate, 5 mol% of [Ni(Pigiphos)(CH₃CN)](BF₄)₂, 5 mol% of base in 1-2 mL of methacrylonitrile at 50 °C, Isolated yields after flash chromatography.  

A homogeneous solution resulted in the presence of DBU, giving the desired product with moderate enantioselectivity in high yield (entry 1). Other bases gave low yields, albeit with a little higher enantioselectivity. For example, the use of bulky TMP, BAS/KOAc, or inorganic base (KOAc) afforded the product with 60% ee, 55% ee, 61% ee, respectively (entries 5-6). Considering both the ee and yield of the reaction together, DBU proved to be so far the best additive.

**Screening Additives II – Chiral Bases**

The nucleophilicity of 1,3-dicarbonyl compounds is improved by base, demonstrating the formation of the corresponding enolate. It is well known that an enamine derived from an amine and a ketone is a stronger nucleophile than the ketone itself. Therefore, we screened a few chiral bases in the 1,4-addition reaction. 5 mol% of S-α,α-diphenylprolinol instead of DBU did improve the enantioselectivity of the 1,4-addition reaction (Scheme 31, 67% ee). The enantiomeric excess is not further improved using up to 50 mol% S-α,α-diphenylprolinol. High enantioselectivity was obtained using (S)-α,α-bis(2-naphthyl)prolinol as a base (66% ee). Interestingly, in the presence of the enantiomer (R)-α,α-bis(2-naphthyl)prolinol the reaction gave very poor selectivity (11% ee). This is obviously the stereochemically mismatched case. Other chiral bases were tested in the reaction to give moderate ee’s (50-57% ee). Although some improvement of enantioselectivity was obtained by using a chiral base as a promotor, the results were not significantly more satisfying than those achieved with DBU.
2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinylnitriles

Scheme 31. Chiral bases promoting the 1,4-addition of 3-methyl-2,4-pentanedione to methacrylonitrile. Reaction conditions: (a) 0.25 mmol substrate, 5 mol% of Ni, 5 mol% of chiral base in 1-2 mL of methacrylonitrile at 50 °C; (b) The yields are isolated and the ee’s were determined by chiral HPLC.

In the absence of Ni complexes the desired product was not formed even when the reaction was run for 15 days at 50 °C using S-α,α-diphenyl-prolinol as a chiral base. This further demonstrates that the Ni(Pigiphos) complex is the crucial activator for vinylnitriles.

Solvents Effects

Table 9. Screening of solvents in the 1,4-addition of 3-methyl-2,4-pentanedione to methacrylonitrile. a

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methacrylonitrile</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>18</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>Acetone</td>
<td>16</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOH</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>Et2O</td>
<td>n.d. (low)</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>toluene (50 °C to 80 °C)</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>CH2Cl2</td>
<td>28</td>
<td>50</td>
</tr>
</tbody>
</table>

a Unless otherwise specified, reactions were performed using 0.25 mmol of substrate, 5 mol% of DBU, 5 mol% of cat [Ni(Pigiphos)(CH3CN)](BF4)2 in 1-2 mL of solvents (methacrylonitrile:solvent = 1:1) at 50 °C; b Isolated yield; c Ee measured by chiral HPLC.

Concerning the solvent the best results were obtained using methacrylonitrile both as a solvent and 1,4-addition acceptor (Table 9, entry 1, 50% ee, in 60% yield). When performing
the reaction in acetonitrile the ee was slightly higher, but the reaction was very sluggish (entry 2, 53% ee, in 18% yield). In other polar solvents such as THF, acetone, or tert-butanol, the reaction proceeded slowly and the enantioselectivity was low. In nonpolar co-solvents such as ether, or toluene, the solubility of the catalyst was too poor to form homogeneous solutions, and this correlated with low yields and selectivities. Nevertheless, in dichloromethane a comparable ee was obtained, probably because the completely soluble complex efficiently catalyzed the addition reaction (50% ee). However, the low yield (28% yield) can be attributed to a possible scavenging of chloride from CH₂Cl₂ by the dicationic Ni(II)-complex. 53

Effect of Temperature

Our asymmetric conjugate 1,4-addition was performed at different temperatures and it was observed that at 50 °C the complex was slightly more effective (Table 10, entry 3, 50% ee, in 61% yield) than at low temperature (-20 °C). A too high temperature is detrimental to both yield and selectivity (entry 5, at 110 °C, 19% ee and 59% yield).

<table>
<thead>
<tr>
<th>entry</th>
<th>Temperature</th>
<th>reaction time</th>
<th>yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-20</td>
<td>11 d</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>25, (rt)</td>
<td>6 d</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>5 d</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>3 d</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>3 d</td>
<td>54</td>
<td>19</td>
</tr>
</tbody>
</table>

Unless otherwise specified, reactions were performed using 0.25 mmol of substrate, 5 mol% of DBU, 5 mol% of cat [Ni(Pigiphos)(CH₃CN)(BF₄)₂] in 1-2 mL of methacrylonitrile. Isolated yield. "Ee measured by chiral HPLC.

Effects of Counterions

Examination of different counterions shows that ClO₄⁻ or BF₄⁻ give similar enantioselections. Complex with BPh₄⁻ as counterion afforded lower ee (Table 11).

<table>
<thead>
<tr>
<th>entry</th>
<th>counterion (X)</th>
<th>yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClO₄⁻</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>BF₄⁻</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>BPh₄⁻</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>
Unless otherwise specified, reactions were performed using 0.25-0.5 mmol of substrate, 5 mol% of catalyst [Ni(Pigiphos)(CH₃CN)]X₂, 5 mol% of DBU in 1-2 mL of methacrylonitrile, \(^a\) Isolated yield; \(^c\) Ee measured by chiral HPLC.

**Substrate Scope in the 1,4-Addition Reaction of Diketones to Methacrylonitrile**

Optimization experiments revealed the combination of 5 mol% of [Ni(pigiphos)(solvent)](BF₄)₂ (Niₐ), or [Ni(pigiphos)(solvent)](ClO₄)₂ (Niₖ), 5 mol% of DBU, at 50 °C, without any co-solvent (methacrylonitrile as a nucleophile and a solvent) as the best reaction conditions. Under these standard conditions, the asymmetric addition of various diketones, including acyclic and cyclic ones, to methacrylonitrile was carried out and the results are summarized in (Table 12).

Reaction with 3-ethyl-2,4-pentanedione S₂₆ afforded higher yield within shorter time, although the enantioselectivity was only moderate (entry 2, 41% ee, 86% yield). The application of the same reaction conditions to other acyclic 1,3-diketones was unsuccessful, as will be discussed later. Conjugate addition of cyclic 1,3-diketones (S₂₇-S₃₀) to methacrylonitrile afforded the corresponding product in good to excellent isolated yields (entries 3-6, 81-99%). Unfortunately, the enantioselectivity of these 1,4-additions remained moderate (21-58% ee).

Conjugate addition of different diketones to methacrylonitrile was realized using [Ni(Pigiphos)(CNMe)](ClO₄)₂ as a catalyst generated in situ or with isolated complexes Niₖ. The results are summarized in Table 8. It is further demonstrated that the C-C bond-forming reaction is not strongly affected by different counterions of the Ni(II) complex, i.e. with variations enantioselectivities in the range of ±3-9% ee.

Additionally, 2-ethyl-1,3-pentanediione was chosen as an example of cyclic diketone for the conjugate addition to methacrylonitrile under different conditions (entry 5). Using ClO₄⁻ as counter ion, the enantioselectivity improved to 58%. In acetone or 1,2-dichloroethane, no more promising results were obtained (entry 5, 49%, 45% ee respectively). A higher ee was obtained (55% ee) when the conjugate addition was performed at room temperature. The above results demonstrate that the counterion is not an important factor to enantioselection, and the absence of any co-solvent is still a better choice for this type of reaction.
### Table 12. Conjugate addition of various diketones to methacrylonitrile.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S25</td>
<td>P25</td>
<td>5 d</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 d</td>
<td>77&lt;sup&gt;d&lt;/sup&gt;</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>S26</td>
<td>P26</td>
<td>36 h</td>
<td>86</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>S27</td>
<td>P27</td>
<td>40 h</td>
<td>81</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 h</td>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>S28</td>
<td>P28</td>
<td>24 h</td>
<td>99</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 h</td>
<td>80&lt;sup&gt;d&lt;/sup&gt;</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>S29</td>
<td>P29</td>
<td>23 h</td>
<td>99</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 h</td>
<td>85&lt;sup&gt;d&lt;/sup&gt;</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 h</td>
<td>42&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 h</td>
<td>43&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 h</td>
<td>42&lt;sup&gt;d,f,g&lt;/sup&gt;</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>S30</td>
<td>P30</td>
<td>30 h</td>
<td>92</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 h</td>
<td>99&lt;sup&gt;d&lt;/sup&gt;</td>
<td>27</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless otherwise specified, reactions were performed using 0.5 mmol of substrate, 5 mol% of DBU, 5 mol% of cat [Ni(Pigiphos)(CH<sub>3</sub>CN)](BF<sub>4</sub>)<sub>2</sub> in 1-2 mL of methacrylonitrile at 50 °C. <sup>b</sup> Isolated yield. <sup>c</sup> Ee measured by chiral HPLC. <sup>d</sup> catalyst is [Ni(Pigiphos)(NCMe)](ClO<sub>4</sub>)<sub>2</sub> Ni<sub>0</sub> or prepared in situ from 5 mol% of [Ni(H<sub>2</sub>O)](ClO<sub>4</sub>)<sub>2</sub> and 5 mol% of Pigiphos; <sup>e</sup> in acetone; <sup>f</sup> 1,2-Dichloroethane; <sup>g</sup> at room temperature.
2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinylnitriles

2.2.3 1,4-Addition of 1,3-Dicarbonyl Compounds to Acrylonitrile

Acrylonitrile, the most reactive vinylnitrile, is as a Michael acceptor comparable to unsaturated carbonyl compounds such as α,β-unsaturated aldehydes and ketones. However, catalytic enantioselective 1,4-addition towards acrylonitrile remains uncovered. We therefore attempted the conjugate addition of 1,3-dicarbonyl compounds to acrylonitrile using our Ni catalysts. The desired adducts with a chiral quaternary carbon were obtained in high yield but with very low enantioselectivities.

Optimization of 1,4-Addition Reaction to Acrylonitrile

In the absence of a nickel complex and under mild basic conditions 1,4-addition of β-keto ester S31 to acrylonitrile does not proceed even when the reaction mixture is stirred for 5 days at room temperature (Table 13, entry 1).

Table 13. 1,4-Addition of tert-butyl 2-cyclopentanone carboxylate to acrylonitrile.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat (mol%)</th>
<th>Conditions</th>
<th>time</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(0)</td>
<td>DBU, 5 mol%, r.t.</td>
<td>5 d</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ni&lt;sub&gt;A&lt;/sub&gt;, (5)</td>
<td>DBU, 5 mol%, r.t.</td>
<td>2 d</td>
<td>89/4.6</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>Ni&lt;sub&gt;A&lt;/sub&gt;, (5)</td>
<td>r.t.</td>
<td>2 d</td>
<td>54/23</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Ni&lt;sub&gt;A&lt;/sub&gt;, (5)</td>
<td>DBU, 5 mol%, 50 °C</td>
<td>15 h</td>
<td>80/n.d.</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Ni&lt;sub&gt;E&lt;/sub&gt;, (5)</td>
<td>DBU, 5 mol%, r.t.</td>
<td>2 d</td>
<td>84/16</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>Ni&lt;sub&gt;F&lt;/sub&gt;, (5)</td>
<td>DBU, 5 mol%, r.t.</td>
<td>2 d</td>
<td>98/0</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless otherwise specified, reactions were performed using 0.25-0.5 mmol of substrate, 5 mol% of base, 5 mol% of cat in 1-2 mL of acrylonitrile at room temperature; <sup>b</sup> Isolated yield; <sup>c</sup> Ee measured by chiral HPLC.

In the presence of catalytic amounts of a dicationic nickel complex (Ni<sub>A</sub>) and 5 mol% of DBU at room temperature the desired product was formed readily, albeit with low enantioselectivity (entry 2, 14% ee). We also isolated a small amount of product P31b (4.6%), which was formed by a second conjugate 1,4-addition of P31a to acrylonitrile. In the absence of any basic additive, the same reaction proceeded smoothly using complex Ni<sub>A</sub> as the catalyst, however, giving more P31b (entry 3. 23%). Increasing the temperature to 50 °C, the reaction took place efficiently without affecting the enantioselectivity (entry 4, 15% ee, in 80% yield). Unfortunately, sterically hindered complexes (Ni<sub>E</sub> or Ni<sub>F</sub>) used as catalysts in the
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

1,4-addition to acrylonitrile in the presence of DBU, afforded the desired product with lower enantioselectivity, albeit in high yield (entries 5, 6, 12% or 7% ee). Again, [Ni(Pigiphos)]^{2+} proves to be the most effective catalyst in 1,4-addition to alkenenitriles. A basic additive is again crucial to drive the reaction to completion giving the single adduct P31a. We surveyed a variety of bases also in this 1,4-addition reaction, including achiral and chiral bases (Table 14) and we found that in the presence of the sterically crowded base TMP poor enantioselectivity was obtained (entry 1, 8% ee, in 89% yield), whereas DABCO was detrimental to the activity. The combination of the nickel catalyst and a base is necessary for the conjugate addition to acrylonitrile to occur. However, even chiral bases did not affect the enantioselectivity significantly (entries 3-8). The newly formed stereogenic carbon is in the a-position of the β-keto ester, and thus always remote from the chiral environment of the nickel complex, resulting in an inefficient transfer of chirality.

Table 14. Screening bases in the 1,4-addition of tert-butyl 2-cyclopentanone carboxylate to acrylonitrile.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>cat (mol%)</th>
<th>Basic additive</th>
<th>yield (%)(^b) P31a/P31b</th>
<th>ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(_{A}) (5)</td>
<td>TMP</td>
<td>89/n.d.</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Ni(_{A}) (5)</td>
<td>DABCO</td>
<td>low</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>Ni(_{A}) (5)</td>
<td>(R)-bis(2-naphthalyl)prolinol</td>
<td>78/0</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Ni(_{A}) (5)</td>
<td>(S)-bis(2-naphthalyl)prolinol</td>
<td>97/0</td>
<td>&lt;10</td>
</tr>
<tr>
<td>5</td>
<td>Ni(_{A}) (5)</td>
<td>(S)-diphenylprolinol</td>
<td>99/0</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Ni(_{A}) (5)</td>
<td>(S)-diphenylprolinol</td>
<td>96/0</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>Ni(_{A}) (5)</td>
<td>(S,S)-TsDPEN</td>
<td>96/0</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise specified, reactions were performed using 0.25-0.5 mmol of substrate, 5 mol% of base, 5 mol% of cat in 1-2 mL of acrylonitrile at room temperature; \(^b\) Isolated yield; \(^c\) Ee measured by chiral HPLC; \(^d\) A mixture of 1:1 CH\(_2\)Cl\(_2\):acrylonitrile as solvent.

The scope of the 1,4-Addition Reaction to Acrylonitrile

Optimization of the 1,4-addition to acrylonitrile showed the reaction to proceed smoothly under basic condition in the presence of a nickel complex at room temperature, giving high yield but poor enantioselectivity. The scope of the substrate in this conjugate addition reaction
was extended to acyclic and cyclic 1,3-dicarbonyl compounds and the results are summarized in Table 15.

Table 15. 1,4-Addition reaction of various 1,3-dicarbonyl compounds to acrylonitrile.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Product</th>
<th>time</th>
<th>yield (%)(^b)</th>
<th>ee a/b (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S32</td>
<td>P32</td>
<td>31 h</td>
<td>66/n.d.</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>S33</td>
<td>P33</td>
<td>21 h</td>
<td>69/n.d.</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>S31</td>
<td>P31</td>
<td>31 h</td>
<td>89/4.6</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>S34</td>
<td>P34</td>
<td>34 h</td>
<td>72/23</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>S35</td>
<td>P35</td>
<td>17 h</td>
<td>92/n.d.</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>S36</td>
<td>P36</td>
<td>4 h</td>
<td>94/n.d.</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>S37</td>
<td>P37</td>
<td>8 h</td>
<td>96/0</td>
<td>12</td>
</tr>
</tbody>
</table>
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

Unless otherwise specified, reactions were performed using 0.25-0.5 mmol of substrate, 5 mol% of basic additive, 5 mol% of cat in 1-2 mL of acrylonitrile at room temperature. Yields isolated after chromatography. Ee measured by chiral HPLC, only ee of product a.

Treatment of ethyl acetoacetate with acrylonitrile under standard conditions afforded the racemic compound P32 in good yield (entry 1). The sterically unencumbered β-keto ester might be the reason for the absence of enantioselectivity. The bulkier β-keto ester S33 gave some enantioselectivity (entry 2, 18% ee). However, the reaction of the more sterically hindered tert-butyl ester S21 with acrylonitrile afforded the product without a significant improvement of enantioselection. A series of cyclic β-keto esters S34-S37 reacted with acrylonitrile affording the corresponding products in high yields, however, again with low enantioselectivities (entries 4-7, 5-19% ee).

Additionally, a diketone was treated with acrylonitrile in the presence of 5 mol% of a dicationic nickel complex and 5 mol% of DBU at room temperature to afford the corresponding product P38 in 90% yield without enantioselection (Scheme 32). Treating the identical diketone with methacrylonitrile did not give any product. This phenomenon clearly showed the inertness of methacrylonitrile in comparison to acrylonitrile. We did not expand the scope of the reaction to other asymmetric diketones due to the poor enantioselection.

![Scheme 32](image)

Scheme 32. 1,4-Addition of a diketone to acrylonitrile.

2.2.4 Scope and Limitations of Donors and Acceptors

2.2.4.1 Limitations of Nucleophiles

Carbon Nucleophile

Various α-unsubstituted-1,3-diketones were employed in the conjugate 1,4-addition to methacrylonitrile but were not successful. It is not clear why this type of diketones show less reactivity than unsubstituted β-keto ester (Scheme 33, A, B, C).
2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinylnitriles

As the α-substituted form of A, namely, 2-methyl-1,3-pentanediolone is an active donor towards methacrylonitrile, we expected that the sterically hindered 2-methyl-2,2,6,6-tetramethyl-1,3-diketone D would react with methacrylonitrile to afford product with higher enantioselectivity. Unfortunately, no adduct was formed and this may be due to too bulky t-Bu groups. The less bulky 1,3-diphenyl-3-methyl 1,3-diketone E does not react with methacrylonitrile, presumably due to the highly conjugated system of the corresponding enolate resulting in a poor nucleophile. Subsequently, a less conjugated system generated from an unsymmetric diketones F was tried, but did not afford the addition product. Since cyclic diketones are more active than open-chain diketones, diketones G, H, and I were examined as a mixed form (i.e. α-acetylated cyclic ketones) in the 1,4-addition reaction. Strangely, no adduct was formed in the reaction and the substrate were recovered unchanged.

Other than 1,3-diketones as 1,4-addition donors, some other type of nucleophiles were attempted in the addition reaction to methacrylonitrile. 2-Nitropropane did not show any reactivity, whereas phenylacetylene K was found to be only a poor donor towards methacrylonitrile. Even after deprotonation by a base it remains a poor nucleophile. A Grignard reagent L was tested at temperature between -20 and 0 °C to show no reactivity. Thus, most of the attempted reagents failed at extending the scope of the nucleophiles in the 1,4-addition to methacrylonitrile, showing how challenging this reaction is.

Sulfur and Oxygen Nucleophiles

Being good Michael donor both oxygen and sulfur nucleophilies were tested in the addition reaction to methacrylonitrile under standard reaction conditions. In the presence of a
dicationic Ni(II)-Pigiphos complex (NiA) and DBU, thiophenol reacted with methacrylonitrile at 50 °C to afford the racemic P39 in low yield (Table 16, entry 1, 11%). No ee was observed even when the reaction proceeded at room temperature albeit in high yield (entry 2, 66%). Excess DBU led to the formation of the racemic product P39 in high yield (entry 3, 99% yield). In the absence of nickel-complex a smooth and clean reaction was observed when thiophenol was reacted with methacrylonitrile to afford the adduct in quantitative yield. On the other hand, in the absence of base the reaction did not take place even in the presence of 10 mol% of Ni-complex (entries 5, 6). This observation shows that the addition reaction of thiophenol to methacrylonitrile can be realized only under basic condition. The corresponding benzenethiolate generated in situ by deprotonation of thiophenol by DBU is either a strong nucleophile, which can be shown by the attack to methacrylonitrile to complete the 1,4-addition reaction, or acts as a ligand by coordinating to the Ni(II) complex, thus shutting down the reaction. However, in the absence of base the desired product was not obtained probably due to either the weak nucleophilicity of thiophenol, or the catalyst poisoning by the mercapto group. Enantioselective 1,4-addition reaction of thiocompounds to vinylnitriles is still demanding and challenging.

### Table 16. Attempted of 1,4-addition of thiophenol to methacrylonitrile.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>condition</th>
<th>time</th>
<th>yield (%) (^b)</th>
<th>ee (%) (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiA, 5 mol%, DBU, 5 mol%, 50 °C</td>
<td>16 h</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>NiA, 5 mol%, DBU, 5 mol%, r.t.</td>
<td>7 d</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>NiA, 5 mol%, DBU, 1.1 eq, r.t.</td>
<td>18 h</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DBU, 1.1 eq, r.t.</td>
<td>18 h</td>
<td>~99</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>NiA, 5 mol%, r.t.</td>
<td>17 h</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>NiA, 10 mol%, r.t.</td>
<td>3 d</td>
<td>NR</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise specified, reactions were performed using 0.5 mmol of substrate, 5 mol% of DBU, 5 mol% of NiA, ([Ni(Pigiphos)(CH.3CN)(BF4)2] in 1-2 mL of methacrylonitrile at 50 °C; \(^b\) Isolated yield; \(^c\) Ee measured by chiral HPLC.

Phenol was attempted in the addition reaction to methacrylonitrile in the presence of complex NiA. A conversion of 50% was determined by \(^1\)H NMR after the reaction mixture was stirred for one week at 50 °C. The reaction mixture could not be easily purified by chromatography because a trace of phenol always accompanied the desired product P40.
2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinylnitriles

(Scheme 34). This particular enantioselective 1,4-addition reaction of an oxygen nucleophile to an alkenenitrile remains to be explored.

\[
\text{PhOH} + \begin{array}{c}
\text{PhCN} \\
\text{C} = \text{C} \\
\text{CN}
\end{array} \xrightarrow{5 \text{ mol} \% \text{NiA}} \begin{array}{c}
\text{PhO} \\
\text{C} = \text{C} \\
\text{CN}
\end{array} \xrightarrow{5 \text{ mol} \% \text{DBU}} \begin{array}{c}
\text{CN} \\
\text{C} = \text{C} \\
\text{Ph}
\end{array}
\]

Scheme 34. Attempt on the addition reaction of phenol to methacrylonitrile.

2.2.4.2 Limitation of Vinylnitriles

Various alkenenitriles (Scheme 35) were attempted to in the reaction with open-chain and cyclic diketones. Acrylonitrile is a strong Michael acceptor and is commonly utilized in traditional Michael addition reaction. However, conjugate addition of 1,3-dicarbonyl compounds to acrylonitrile catalyzed by Ni(II)-Pigiphos complex gave quite low enantioselectivity. Methacrylonitrile is a weaker Michael acceptor and is not often used as such. As shown above the enantioselective conjugate addition to methacrylonitrile catalyzed by a dicationic Ni(II) catalyst yielded moderate enantioselectivity. Even though substituted vinylnitriles containing non activating substituents are very inactive due to their electronic properties and steric hindrance, we extended the addition reaction to a few substituted vinylnitriles, including some with activating substituents (Scheme 35). We choose acyclic diketones, cyclic diketones, or β-keto esters (Scheme 36) as conjugate addition donors to test in the addition reaction vinylnitriles.

Scheme 35. Various vinylnitriles.

![Scheme 36. 1,3-Dicarbonyl compounds used as donors in attempted addition for various vinylnitrile](image-url)
2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

Unfortunately, very limited success was achieved using simple substituted vinylnitrile, i.e., when no other functional group is attached to the vinylnitrile moiety. α-Pentylacrylonitrile was inert to the conjugate addition whereas the more active α-phenylacrylonitrile itself readily polymerizes, rather than undergoing conjugate addition with acyclic or cyclic diketones. Conjugate addition did not take place at all when other β-substituted acrylonitriles, including a cyclic vinylnitrile, were used as acceptors (second row of Scheme 35). Until now all the vinylnitriles examined are unactivated alkenenitriles.

Since simple vinylnitriles have very low reactivity, activated vinylnitriles were subjected to the 1,4-addition reaction (third row of Scheme 35). α-Acetoxyacrylonitrile is a favored Michael acceptor towards an chiral enamine derived from phenylethylamine and a ketone. In the presence of complex NiA and DBU, α-acetoxyacrylonitrile reacted with 2-ethyl-1,3-cyclopentanedione in acetonitrile at 50 °C to yield unexpectedly the triketone 41 (Scheme 37). The formation of 41 indicates that the nucleophilic attack has taken place either at the α-instead of β-carbon of the nitrile or directly at the acetyl group.

![Scheme 37. An addition reaction to α-acetoxyacrylonitrile.](image)

In order to avoid undesired nucleophilic substitution toward acetoxy group, 2-chloroacrylonitrile was used as a acceptor in the presence of NiA and DBU at 40 °C (Scheme 38) but no addition took place. When DABCO was used at room temperature the desired product 42a was obtained, along with a small amount of an alkene 42b, produced by elimination of HCl (Scheme 38, 42a:42b = 10:1, determined by 1H NMR).

![Scheme 38. 1,4-Addition of a diketone to 2-chloroacrylonitrile](image)

In order to further investigate the reactivity of 2-chloroacrylonitrile, a β-keto ester S31 was employed in the conjugate addition either in the presence of NiA and base or only under basic condition (Scheme 39). The desired product 43 was obtained in good yield under basic condition, rather in the presence of Ni complex. We reasoned that the trace of HCl from 2-chloroacrylonitrile deactivated the Ni(II) catalyst prohibiting the catalytic addition reaction.

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2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinylnitriles

![Scheme 39](image)

Conditions A: DABCO, 20 mol%, CH₂Cl₂, rt: 76%, dr = 1.2:1 (¹H NMR)
Conditions B: Niₐ, 5 mol%, DBU, 5 mol%, CH₂Cl₂, 40 °C: no reaction

Scheme 39. 1,4-Addition of a β-keto ester to 2-chloroacrylonitrile.

2.2.5 Plausible Mechanism of the Addition Reaction

On the base of the observations made for the 1,4-addition reaction and of earlier work in our group on hydroamination and hydrophosphination catalyzed by a dicationic [Ni(Pigiphos)]²⁺ complex, we propose the catalytic cycle is illustrated in Scheme 40. Undoubtedly, activation of methacrylonitrile occurs through coordination of the nitrogen atom of nitrile group rather than of the double bond to the Ni(II) center, as is confirmed by the X-ray analysis of [Ni(Pigiphos)(methacrylonitrile)] X₂ (X = ClO₄⁻, or BF₄⁻ [Niₐ, Niₐ]). The fully characterized complexes Niₐ and Niₐ are active species towards C-C bond formation reactions giving the same yields and enantioselectivities as the catalyst prepared in situ prepared catalyst from [Ni(H₂O)₆](BF₄)₂ and Pigiphos.

![Scheme 40](image)

Scheme 40. A proposed mechanism for conjugate addition of diketone to methacrylonitrile [Ni] = [Ni(Pigiphos)]²⁺.

Thus, the species A is demonstrated to be an intermediate in the catalytic cycle. The activated double bond of methacrylonitrile is involved in a nucleophilic attack by the enolate of the diketone generated through in situ deprotonation by the base, resulting in the proposed intermediate B that can be described as an azaallene-Ni complex C, which is not directly
observed. A stereospecific proton transfer is a key step for the formation of species D containing the new stereogenic center. Preparation of intermediate D by reaction of [Ni(Pigiphos)(THF)](BF₄)₂ with 3-(2-cyanopropyl)-3-methyl-2,4-pentanedione (P₂⁵) in dichloromethane afforded the desired Ni complex D, that was characterized by ¹H- and ³¹P-NMR, MS, and elemental analysis. Unfortunately, attempts to grown single crystals of this complex afforded the derivative [Ni(II)(Pigiphos)(OOCCH₃)]BF₄ whose structure was determined by X-ray crystallography. The origin of the acetate ion under crystallization conditions is unclear at present. However, we can still postulate that the intermediate D is formed, followed by ligand exchange by methacrylonitrile to regenerate the species A, thus closing the catalytic cycle.

2.3 Conclusion

In summary, a group of Pigiphos-type ligands and the corresponding dicationic Ni(II) complexes have been synthesized and the structure of two complexes (Niₐ and Niₐ) was determined by X-ray crystallography. A dicationic [Ni(Pigiphos)(nitrile)]²⁺ (nitrile = P₂⁵) complex D (Scheme 40) was prepared, but could not be obtained in crystalline from.

Enantioselective conjugate addition of 1,3-dicarbonyl compounds to vinylnitriles in the presence of dicationic Ni(II) complexes was explored and optimization of the reaction has been performed by screening various parameters, such as Lewis acids, ligands, bases, solvents, and temperature. Therefore, for the first time metal-catalyzed asymmetric 1,4-addition of 1,3-diketones to methacrylonitrile was realized to afford the desired product in good yields with low to moderate enantioselectivities (ee up to 67%). A quaternary stereogenic carbon center has been constructed through conjugate addition of β-keto esters to acrylonitrile but very low enantioselectivities were obtained (only up to 19% ee). Further improvement of the enantioselectivity of the conjugate addition to vinylnitriles is our future task.
2.4 References


2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles


2. 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinylnitriles


2. 1,4-Addition of 1,3-Dicarbonyl Compound to Vinylnitriles

52 (a) L. Fadini, A. Togni, Chem. Commun. 2003, 30-31. (b) Fadini, L.; Togni, A. Chimia 2004, 58, 208-
58 (a) Murata, K.; Konishi, H.; Ito, M.; Ikariya, T. Organometallics 2002, 21, 253-255. (b) Koike, T.; Ikariya,
3 Experimental Section

General Information.

Techniques
All reactions were carried out under an Argon atmosphere using standard Schlenk techniques or in a glove box (under nitrogen). The solvents used for synthetic and recrystallization purposes were of “puriss p.a.” quality (Fluka AG, Riedel-dehaen or Merck) and were distilled under Argon (THF from Na/benzenphenone; CH₂Cl₂, MeOH, EtOH and acetonitrile from CaH₂; pentane, hexane, toluene and Et₂O from Na; pyridine and triethylamine from KOH).

For flash column chromatography, technical grade solvents were generally used. NMR-solvents for sensitive compounds were cold distilled under Argon (toluene-d₈ and C₆D₆ from Na; CD₂Cl₂ from CaH₂; CDCl₃, acetone, MeOH-d₄ and acetonitrile-d₃ from molecular sieves).

Analytical Techniques and Instruments

TLC: Silica: Merck 60-F254; Alumina: Macherey-Nagel co N/UV254; detection: UV-light (254 nm), mostain (10 g (NH₄)₂[Mo₇O₂₄]·4H₂O, 12 mL H₂SO₄ conc., 190 mL H₂O, 0.4 g Ce(SO₄)₂·nH₂O or KMnO₄/H₂SO₄. FC: Silica: Fluka Kieselgel 60; Alumina: ICN Alumina N Akt. I. NMR: The routine ¹H-, ¹³C- and ¹⁹F-NMR spectra were measured in the given solvent on either a Bruker Avance 200 spectrometer [frequency in MHz: ¹H: 200.13, ¹³C: 50.32 and ¹⁹F: 188.31] or a Bruker Avance 250 spectrometer [frequency in MHz: ¹H: 250.13 and ¹³C: 62.90] or a Bruker Avance 300 spectrometer [frequency in MHz: ¹H: 300.13 and ¹³C: 75.5] at room temperature. The chemical shift are given in ppm relative to TMS, and referenced to the solvent signal for ¹H and ¹³C{¹H}-NMR, relative to an external reference for ¹⁹F{¹H}-[CFCl₃: δ = 0.0 ppm]. MS: Measurements (EI-MS, FAB-MS, MALDI-MS) were performed by the MS-service of the “Laboratorium fuer Organische Chemie der ETHZ”). The signals are given as m/z and the intensity in % of the base peak. EA: Analyses were performed by the micro elemental analysis service of the “Laboratorium fuer Organische Chemie der ETHZ”). IR: Perkin-Elmer-Paragon 1000-FT-IR-Spectrometer; measured in KBr, in Nujol or in CHCl₃; only the characteristic peaks are given in cm⁻¹. HPLC: Agilent Series 1100 or HP 1050 with UV-detector (DAD); flow in mL/min, eluent (hexane:iPrOH-ratio) and wavelengths are given in each experiment; columns: Chiralcel OD-H (4.6 x 250 nm, particle 5 µm), Chiralcel OJ (4.6 x 250 nm, particle 10 µm), Chiralcel OB-H (4.6 x 250 nm, particle 5 µm), Chiralcel AD-H (4.6 x 250 nm, particle 5 µm), Chiralcel DP (4.6 x 250 nm, particle 5 µm), Chiralcel AS (4.6 x 250 nm, particle 5 µm). GC: Fisons Instruments GC 8000 Series or ThermoQuest Trace GC 2000 Series with FID-detector; column α–dex 120 (30 m x 0.25 mm x 0.25 µm), β–dex 120 (30 m x 0.25 mm x 0.25 µm), γ–dex 120 (30 m x 0.25 mm x 0.25 µm). Thermo Finnigan trace MS, EI-MS, column: ZB-5 (30 m x 0.25 mm x 0.25 µm). Polarimeter: Perkin Elimer 341; cell 10 cm, solution in CHCl₃ or in EtOH, 22 °C; c in g/100 mL.

Crystallography: X-ray structural measurements were carried out on a Siemens CCD diffractometer (Siemens SMSAT PLATFORM, with CCD detector, graphite monochromator,
3 Experimental Part

Mo-K-radiation). The program SMART served for data collection. Integration was performed with SAINT. The structure solution (direct methods) was accomplished with SHELXTL 97. Model plots were made with ORTEP32 or CrystalMaker.

Chemicals

RuCl3·3H2O (containing 38-39% Ru) was purchased from Fluuka. (R,R)-TsDPEN ([1R,2R]-(4-Toluenesulfonyl)-1,2-diphenylethlenediamine) and (S,S)-TsDPEN ([1S,2S]-(4-Toluenesulfonyl)-1,2-diphenylethlenediamine) were purchased from Acros. F-TEDA and NCS were purchased from Aldrich. (R)-(+-)[1-(Dimethylamino)ethyl]ferrocene was provided by SOLVIAS AG and was recrystallized as tartrate salt according to the reported literature. Deuterated solvents were purchased from Cambridge Isotope Laboratories (dichloromethane-d2, toluene-d5, acetone-d6, benzene-d6, tetrahydrofurane-d8, acetonitrile-d3, and methanol-d4), ARMAR AG (benzene-d6), and Dr. Glaser AG (chloroform-d). The following compounds were purchased from Aldrich: [Ni(6H2O)][ClO4]2, [Ni(6H2O)][BF4]2. The substrates needed for the catalysis (acrylonitrile and methacrylonitrile) were distilled under Argon in the presence of anhydrous CaCl2. 3-Methyl-2,4-pentanedione and 3-ethyl-2,4-pentanedione were distilled under Argon. All other commercially available chemicals were purchased from Fluuka AG, Aldrich AG, ACROS AG, ABCR and Lancaster and used without further purification.

3.1 Experimental Part of Chapter 1 - Asymmetric Synthesis of α-Fluoro-β-hydroxy Esters and Their Derivatives

Preparation of Catalysts.

Bis(acetonitrile)dichloro[(4R,5R)-2,2-dimethyl-α,α,α',α'-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanolato(2-)-KO,KO']-titanium)

(TiCl2((R,R)-1-Np-TADDOLato)(MeCN)2, or R,R-Ti)((R,R)-1-Np-TADDOLato)(MeCN)2, or R,R-Ti)\(^1\)

TiCl2(OPr)\(_2\) was added to a solution of the corresponding (R,R)-TADDOL in acetonitrile at room temperature. The resulting mixture was stirred overnight and the solvent was removed under HV. The residue was washed three times with hexane to yield a yellowish solid.

\(^1\)H NMR (200 MHz, CDCI3): 0.25 (s, 6H, CH\(_3\)), 1.93 (s, 6H, CH\(_3\)), 6.26 (s, 2H), 6.75 (t, J = 7.6 Hz, 2H), 6.99 (t, J = 8 Hz, 2H), 7.20 (t, J = 7 Hz, 2H), 7.59-7.88 (m, 14H), 8.01 (d, J = 8.6 Hz, 2H), 8.32 (d, J = 7.4 Hz, 2H), 8.90 (d, J = 6.4 Hz, 2H).

Ru(R,R)TsDPEN (R,R-Ru)\(^2\)

A mixture of [RuCl\(_2\)(η\(^6\)-p-cymene)]\(_2\) (306.5 mg, 0.5 mmol), (R,R)-TsDPEN [(1R,2R)-(4-(4-toluenesulfonyl)-1,2-diphenylethlenediamine] (366.4 mg, 1.0 mmol), and KOH (400 mg, 7.1 mmol) in CH\(_2\)Cl\(_2\) (7 mL) was stirred at room temperature for 5 min.
On addition of water (7 mL) to the reaction mixture, the color changed from orange to deep purple. The purple organic layer was washed with water (7 mL), dried over CaH₂, and concentrated to dryness to afford deep purple Ru(1R,2R)-p-TsNCH(C₆H₅)CH(C₆H₅)NH)(tfc-p-cymene) (536 mg, 87%).

**¹H NMR** (300 MHz, CDCl₃): δ 1.25, 1.31 (each d, J = 6.9 Hz, 3H, CHMe₂), 2.21 (s, 3H, CH₃ in p-cymene), 2.29 (s, 3H, CH₃ in Ts), 2.62-2.69 (m, 1H, CHMe₂), 4.00 (d, J = 4.8 Hz, HCNH), 4.45 (s, 1H, HCN-p-Ts), 5.31, 5.36, 5.53, 5.71 (each d, J = 5.7 Hz, 1H, CHarom in p-cymene), 6.88, 7.30 (each d, J = 8 Hz, 2H, CHarom in p-Ts), 7.07-7.42 (m, 10H, p-TsNCH(C₆H₅)CH(C₆H₅)NH).

**Ru(S,S)TsDPEN (S,S-Ru)**

A mixture of (RuCl₂(η⁶-p-cymene))₂ (306.5 mg, 0.5 mmol), (S,S)-TsDPEN [(1S,2S)-(+)N-(4-toluenesulfonyl)-1,2-diphenylethylene diamine] (366.4 mg, 1.0 mmol), and KOH (400 mg, 7.1 mmol) in CH₂Cl₂ (7 mL) was stirred at room temperature for 5 min. On addition of water (7 mL) to the reaction mixture, the color changed from orange to deep purple. The purple organic layer was washed with water (7 mL), dried over CaH₂, and concentrated to dryness to afford deep purple S,S-Ru in quantitative yield.

**¹H NMR** (300 MHz, CD₂Cl₂): δ 1.24, 1.32 (each d, J = 6.6 Hz, 3H, CHMe₂), 2.20 (s, 3H, CH₃ in p-cymene), 2.32 (s, 3H, CH₃ in Ts), 2.62-2.69 (m, 1H, CHMe₂), 3.98 (d, J = 4.8 Hz, HCNH), 4.45 (s, 1H, HCN-p-Ts), 5.31, 5.32, 5.58, 5.75 (each d, J = 6.3 Hz, 1H, CHarom in p-cymene), 6.92, 7.47 (each d, J = 7.5 Hz, 2H, CHarom in p-Ts), 7.02-7.29 (m, 10H, p-TsNCH(C₆H₅)CH(C₆H₅)NH).

**Ru(R,R)TsDPEN-HCl (R,R-Ru-HCl)**

A mixture of [RuCl₂(η⁶-p-cymene)]₂ (110 mg, 0.18 mmol), (R,R)-TsDPEN [(1R,2R)-(+)N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine] (132 mg, 0.36 mmol), and Et₃N (0.1 mL, 0.72 mmol) in 2-propanol (2 mL) was stirred at 80 °C for 1 h. The orange solution was concentrated and filtered to give an orange solid, which was washed with a small amount of water. The resulting Ru,Ru-HCl orange powder was dried under HV (208 mg, 89%).

**¹H NMR** (300 MHz, CDCl₃): δ 1.43, 1.53 (each d, CHMe₂), 2.24 (s, 3H, CH₃ in p-cymene), 2.42 (s, 3H, CH₃ in Ts), 3.11 (m, 2H, CHMe₂ and NHH), 3.62 (m, HCNH₂), 3.82 (m, 1H, HCN-p-Ts), 5.59-5.70 (m, 4H, CHarom in p-cymene), 6.63 (m, 1H, NHH), 6.73-7.23 (m, 14H, p-CH₃C₆H₄SO₂N, CH(C₆H₅)CH(C₆H₅)NH).

**Non-chiral-Ru**

A mixture of N-p-toluenesulfonylethylenediamine (0.22 g, 1.0 mmol), [RuCl₂(p-cymene)]₂ (0.31 g, 0.5 mmol) and KOH (0.40 g, 7.1 mmol) in dichloromethane (7 mL) was stirred for 5 min at room temperature. Water (7
3. Experimental Part

mL) was added and the two layers were separated. The organic layer was washed with water (7 mL) and dried over CaH₂. The solvent was removed in vacuo to give a purple powder (0.35 g, 77%).

^1H NMR (300 MHz, CDCl₃): δ 1.23 (d, 6H, J = 6.9 Hz, {p-cymene}CH(CH₃)₂), 2.32 (s, 3H, {p-cymene}CH₃), 2.40 (s, 3H, {p-tosyl}CH₃), 2.75 (b, 2H, CH₂NH₂), 2.83 (m, 1H, {p-cymene}CH(CH₃)₂), 3.02 (b, 2H, TosNC₂), 5.50 (b, 2H, 2{p-cymene}Hortho), 5.70 (b, 2H, 2{p-cymene}Hortho), 7.25 (d, 2H, J = 8.4 Hz, 2{p-tosyl}Hmeta), 7.73 (d, 2H, J = 8.4 Hz, 2{p-tosyl}Hmeta).

Preparation of Racemic α-Fluoro-β-keto Esters and α-Chloro-β-keto Esters³

General Procedure
CpTiCl₃ (5 mol%) was added to a solution of β-keto ester in acetonitrile and the mixture was stirred until a clear yellow solution was obtained. To this was added F-TEDA (or NCS) (1.1 eq), and the reaction mixture was stirred until complete conversion (TLC), followed by extraction with TBME. The organic phase was dried over MgSO₄ and evaporated. The residue was purified by flash chromatography to give the product.

Ethyl 2-fluoro-2-methyl-3-oxo-3-phenylpropanoate (S1)

CpTiCl₃ 16 mg, 0.07 mmol, 5 mol%
Substrate 300 mg, 1.45 mmol
F-TEDA 596 mg, 1.68 mmol, 1.12 eq
Acetonitrile 8 mL
Purification (FC) hexane:TBME 15:1
Product 315 mg, 97%

C₁₂H₁₃FΟ₃ (Mᵣ = 224.23). Rᵣ (hexane:TBME 10:1) = 0.31 (UV, KMnO₄). ^1H NMR (200 MHz, CDCl₃): δ 1.20 (t, J = 7.2 Hz, 3H), 1.89 (d, J = 2.2 Hz, 3H), 4.25 (qd, J = 7.2, 1.0 Hz, 2H), 7.43-7.50 (m, 2H), 7.55-7.60 (m, 1H), 8.02-8.07 (m, 2H); ^19F NMR (188.13 MHz, CDCl₃): δ -151.7 (qt, J = 22, 1.7 Hz).

Benzyl 2-fluoro-2-methyl-3-oxobutanoate (S2)

CpTiCl₃ 111 mg, 0.5 mmol, 5 mol%
Substrate 2.07 g, 10 mmol
F-TEDA 3.39 g, 11.3 mmol, 1.12 eq
Acetonitrile 50 mL
Purification (FC) hexane:TBME 5:1
Product 1.45 g, 66.5%

C₁₁H₁₃FO₃ (Mᵣ = 224.23). Rᵣ (hexane:TBME 5:1) = 0.45 (UV, Mostaine). ^1H NMR (300 MHz, CDCl₃): δ 1.70 (d, J = 22.2 Hz, 3H, CH₃), 2.28 (d, J = 4.6 Hz, 3H, CH₃CO), 5.24 (s, 2H, CH₂), 7.35 (m, 5H, Ph); ^19F NMR (188.3 MHz, CDCl₃): δ -156.97 (qq, J = 22.2, 4.7 Hz).
3. Experimental Part

Phenyl 2-fluoro-2-methyl-3-oxo-pentanoate (S3)

CpTiCl3  22 mg, 5 mol%
Substrate  412 mg, 2 mmol
F-TEDA  822 mg, 2.32 mmol, 1.16 eq
Acetonitrile  20 mL
Purification (FC)  hexane:TBME 10:1
Product  342 g, 82%

C_{13}H_{15}FO_{4} (M_r = 254.254). R_f (hexane/TBME 5:1) = 0.3 (Mostaine). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): δ 1.15 (t, J = 7.0 Hz, 3H, CH\textsubscript{3}), 1.83 (d, J = 22.2 Hz, 3H, CH\textsubscript{3}), 2.82 (dq, J = 7.3, 3.0 Hz, 2H, CH\textsubscript{2}), 7.08-7.12 (m, 2H, Ar), 7.25-7.30 (m, 1H, Ar), 7.36-7.44 (m, 2H, Ar); \textsuperscript{19}F NMR (188.31 MHz, CDCl\textsubscript{3}): δ -159.15 (qd, J = 22.2, 3.0 Hz).

4-Methoxyphenyl 2-fluoro-2-methyl-3-oxo-pentanoate (S4)

CpTiCl3  69.6 mg, 0.32 mmol, 5 mol%
Substrate  1.5 g, 6.35 mmol
F-TEDA  2.61 g, 7.36 mmol, 1.16 eq
Acetonitrile  20 mL
Purification (FC)  hexane:TBME 20:1 to 10:1
Product  1.42 g, 88%

C_{13}H_{15}FO_{4} (M_r = 254.254). R_f (hexane/TBME 5:1) = 0.47 (Mostaine). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): δ 1.14 (t, J = 7.2 Hz, 3H, CH\textsubscript{3}), 1.82 (d, J = 22.2 Hz, 3H, CH\textsubscript{3}), 2.74-2.87 (m, 2H, CH\textsubscript{2}), 3.76 (s, 3H, CH\textsubscript{3}), 6.85-6.92 (m, 2H, Ar), 6.99-7.05 (m, 2H, Ar); \textsuperscript{19}F NMR (188.31 MHz, CDCl\textsubscript{3}): δ -159.01 (qt, J = 22, 3.0 Hz).

Diphenylmethyl 2-fluoro-2-methyl-3-oxo-pentanoate (S5)

CpTiCl3  37 mg, 0.17 mmol, 5 mol%
Substrate  1 g, 3.37 mmol
F-TEDA  1.38 g, 3.91 mmol, 1.16 eq
Acetonitrile  20 mL
Purification (FC)  hexane:TBME 50:1
Product  600 mg, 57%

C_{19}H_{19}FO_{2} (M_r = 314.351). R_f (Hexane/TBME 5:1) = 0.47 (Mostaine). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): δ 1.05 (t, J = 7.2 Hz, 3H, CH\textsubscript{3}), 1.77 (d, J = 22 Hz, 3H, CH\textsubscript{3}), 2.61-2.72 (m, 2H, CH\textsubscript{2}), 7.36 (m, 10H, Ar); \textsuperscript{19}F NMR (188.31 MHz, CDCl\textsubscript{3}): δ -159.2 (qt, J = 22, 3.0 Hz).

(2,4,6-Triisopropylbenzyl)-2-fluoro-2-methyl-3-oxopentanoate (S6)

CpTiCl3  35.9 mg, 0.14 mmol, 5 mol%
Substrate  1 g, 2.9 mmol
F-TEDA  1.15 g, 3.2 mmol, 1.16 eq
Acetonitrile  15 mL
Purification (FC)  hexane:TBME 15:1
Product  920 mg, 87%
3. Experimental Part

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.03 (t, $J = 7.2$ Hz, 3H), 1.22 (d, $J = 6.9$ Hz, 6H, Me$_2$CH), 1.23 (d, $J = 6.9$ Hz, 6H, Me$_2$CH), 1.26 (d, $J = 6.9$ Hz, 6H, Me$_2$CH), 1.67 (d, $J = 22$ Hz, Me), 2.63 – 2.78 (m, 2H, CH$_2$CH$_3$), 2.89 (septet, $J = 6.9$ Hz, 1H, CHMe$_2$), 3.12 (septet, $J = 6.9$ Hz, 2H, 2CHMe$_2$), 5.33 (s, CH2O, 2H), 7.04 (s, 2Ar); $^{19}$F NMR (188.13 MHz, CDCl$_3$): $\delta$ -158.645 - 159.005 (m).

tert-Butyl 1-fluoro-2-oxo-cyclopentanecarboxylate (S7)

CpTiCl$_3$ 32.3 mg, 0.15 mmol, 5 mol%
Substrate 542.2 mg, 2.9 mmol
F-TEDA 1.21 g, 3.41 mmol, 1.16 eq
Acetonitrile 20 mL
Purification (FC) hexane:TBME 9:1
Product 417.3 mg, 70%

C$_{10}$H$_{17}$FO$_3$ (Mr = 204.24). R$_f$ (hexane/TBME 5:1) 0.31 (Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.47 (s, 9H, CH$_3$), 2.06-2.16 (m, 2H), 2.19-2.36 (m, 1H), 2.44-2.59 (m, 3H); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -162.7 (dd, $J = 24.7$, 21.7 Hz).

2-Fluoro-2-ethoxycarbonyl-cyclohexanone (8)

CpTiCl$_3$ 64 mg, 0.29 mmol, 5 mol%
Substrate 1.0 g, 5.88 mmol
F-TEDA 2.415 g, 6.82 mmol, 1.16 eq
Acetonitrile 30 mL
Purification (FC) hexane:ethyl acetate 4:1
Product 980 mg, 86%

C$_9$H$_{13}$FO$_3$ (Mr = 188.1961). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.36 (d, $J = 7.2$ Hz, 3H, CH$_3$), 1.80-2.08 (m, 5H), 2.15-2.78 (m, 3H), 4.34 (q, $J = 7.2$ Hz, 2H, CH$_2$CH$_3$); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -160.79 (ddd, $J = 19.4$, 13.8, 5.2 Hz).

2-Acetyl-2-fluorobutyrolactone (3-Acetyl-3-fluorodihydro-2(3H)-furanone) (S9)

TiCl$_4$ 49 µL, 47 mg, 0.25 mmol, 5 mol%
Substrate 542 µL, 640 mg, 5.0 mmol
F-TEDA 2.05 g, 5.88 mmol, 1.16 eq
Acetonitrile 30 mL
Purification (FC) hexane:TBME 2:1
Product 482 mg, 66%

C$_{9}$H$_{17}$FO$_3$ (Mr = 146.116). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 2.45 (d, $J = 4.5$ Hz, 3H, CH$_3$), 2.46-2.72 (m, 1H, CH$_2$), 2.81-2.94 (m, 1H, CH$_2$), 4.41-4.57 (m, 2H, CH$_2$O); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -162.59 to -162.74 (m).

3-Acetyl-3-fluoro-1-phenyl-2-pyrrolidinone (S10)

CpTiCl$_3$ 21.9 mg, 0.1 mmol, 5 mol%
Substrate 406 mg, 2 mmol
3. Experimental Part

F-TEDA
821.9 mg, 2.32 mmol, 1.16 eq

Acetonitrile
10 mL

Purification (FC)
hexane:TBME 3:1

Product
424 mg, 96 %

\( \text{C}_{12} \text{H}_{12} \text{FNO}_2 \) (\( M_r = 221.23 \)). R\(_f\) (hexane/TBME 1:1) = 0.43 (UV, KMnO\(_4\)). \( ^{1} \text{H NMR} \) (300 MHz, CDCl\(_3\)): \( \delta \) 2.26-2.45 (m, 1H), 2.47 (d, \( J = 4.8 \) Hz, 3H, CH\(_3\)), 2.78-2.90 (m, 1H), 3.85-4.02 (m, 2H), 7.21-7.25 (m, 1H), 7.37-7.43 (m, 2H), 7.60-7.63 (m, 2H); \( ^{19} \text{F NMR} \) (188.3 MHz, CDCl\(_3\)): \( \delta \) -157 - -157.3 (m).

Preparation of Racemic \( \alpha \)-Chloro-\( \beta \)-keto Esters, \( \alpha \)-Hydroxy-\( \beta \)-keto Esters and \( \alpha \)-Hydroxy-\( \beta \)-keto Amides:

Ethyl 2-chloro-2-methyl-3-oxo-3-phenylpropanoate (S11)

\( \text{CpTiCl}_3 \)
58 mg, 0.07 mmol, 5 mol%

Substrate
1.1 g, 5.3 mmol

NCS
815 mg, 6.1 mmol, 1.15 eq

Acetonitrile
20 mL

Purification (FC)
hexane:TBME 15:1

Product
1.26 g, 95 %

\( \text{C}_{12} \text{H}_{13} \text{ClO}_3 \) (\( M_r = 240.683 \)). R\(_f\) (hexane:TBME 15:1) = 0.25 (UV, KMnO\(_4\)). \( ^{1} \text{H NMR} \) (250 MHz, CDCl\(_3\)): \( \delta \) 1.09 (t, \( J = 7.2 \) Hz, 3H), 2.01 (s, 3H, CH\(_3\)), 4.20 (q, \( J = 7.2 \) Hz, 2H), 7.43 (t, \( J = 7.4 \) Hz, 2H), 7.55 (d, \( J = 7.2 \) Hz, 1H), 7.99 (d, \( J = 7.6 \) Hz, 2H).

Benzyl 2-chloro-2-methyl-3-oxobutanoate (S12)

\( \text{CpTiCl}_3 \)
11.1 mg, 0.5 mmol, 5 mol%

Substrate
206 mg, 1 mmol

NCS
1.16 eq

MeCN
50 mL

Purification (FC)
hexane:TBME 15:1

Product
180 mg, 75%

\( \text{C}_{12} \text{H}_{13} \text{ClO}_3 \) (\( M_r = 240.683 \)). R\(_f\) (hexane:TBME 3:1) = 0.69 (KMnO\(_4\)). \( ^{1} \text{H NMR} \) (300 MHz, CDCl\(_3\)): \( \delta \) 1.84 (s, Me), 2.30 (s, MeCO), 5.22 (d, \( J = 12 \) Hz, PhCH\(_2\)), 5.26 (d, \( J = 12 \) Hz, PhCH\(_2\)), 7.31-7.41 (m, 5H, Ar).

Diphenylmethyl 2-chloro-3-oxo-2-methylpentanoate (S13)

\( \text{CpTiCl}_3 \)
11 mg, 0.05 mmol, 5 mol%

Substrate
296.4 mg, 1 mmol

NCS
153.6 mg, 1.15 eq

Acetonitrile
7 mL

Purification
FC, hexane:TBME 15:1

Product
oil, 307 mg, 94%
3. Experimental Part

**C\textsubscript{19}H\textsubscript{19}ClO\textsubscript{3} (M\textsubscript{r} = 330.81).** R\textsubscript{f} (hexane/TBME 5:1) = 0.59 (UV, Mostain). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta 1.01 (t, J = 7.2 \text{ Hz}, 3\text{H}, \text{CH}_3\text{CH}_2), 1.86 (s, 3\text{H}, \text{CH}_3), 2.48 (dq, J = 18.3, 7.2 \text{ Hz}, 1\text{H}, \text{CH}_2\text{CH}_3), 2.73 (dq, J = 18.3, 7.2 \text{ Hz}, 1\text{H}, \text{CH}_2\text{CH}_3), 6.91 (s, 1\text{H}, \text{CHPh}_2), 7.26-7.38 (m, 10\text{H}, 2\text{Ar}).

**Ethyl 2-chloro-2-fluoro-3-phenyl-3-oxopropanoate (S14)**

To a solution of ethyl 2-fluoro-3-phenylpropanoate (540 mg, 2.57 mmol) in 15 mL of toluene was added CpTiCl\textsubscript{3} (28.2 mg, 0.13 mmol, 5 mol%) and triethylamine (285.8 mg, 394 \(\mu\)L, 2.83 mmol, 1.1 eq). The mixture was stirred 10 min resulting in a clear solution and 4-(dichloroiodo)toluene (817.3 mg, 2.83 mmol, 1.1 eq) was added. The reaction was monitored by TLC and \textsuperscript{1}H NMR. The reaction was quenched by addition of 50 mL of TBME and the suspension was filtered through celite. The organic phase was washed with NaHC\textsubscript{3}O\textsubscript{3} and brine, dried over MgSO\textsubscript{4}. Flash chromatography on silica gel (hexane:TBME 10:1) gave the product as colorless oil (437 mg, 70%).

**C\textsubscript{11}H\textsubscript{10}ClFO\textsubscript{3} (Mr = 224.65).** R\textsubscript{f} (hexane/TBME 5:1 = 0.51 (UV, Mostaine). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \(\delta 1.28 (t, J = 7.2 \text{ Hz}, 3\text{H}, \text{CH}_2\text{CH}_3), 4.37 (q, J = 7.2 \text{ Hz}, 2\text{H}, \text{CH}_3\text{CH}_2), 7.54 (t, J = 7.7 \text{ Hz}, 2\text{H}, \text{Ph}), 7.66 (t, J = 7.4 \text{ Hz}, 1\text{H}, \text{Ph}), 8.08 (d, J = 8.0 \text{ Hz}, 2\text{H}, \text{Ph}), \textsuperscript{19}F NMR (188.3 MHz, CDCl\textsubscript{3}): \(\delta -116.58 (s).

**2-tert-Butoxycarbonyl-2-hydroxycyclopentanone (S15)**

3-(4-Nitrophenyl)-2-(phenylsulfonyl)-oxaziridine (63) (1.7 g, 5.6 mmol, 1.1 eq) was added to a mixture of tert-buty-2-oxo-cyclopentanecarboxylate (884 mg, 4.8 mmol) and AlCl\textsubscript{3} (32 mg, 5 mol%) in 25 mL of toluene at room temperature. The mixture was stirred overnight and filtered. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 4:1) giving the product a colorless oil (654 mg, 67.1%).

**C\textsubscript{10}H\textsubscript{16}O\textsubscript{4} (Mr = 200.232).** R\textsubscript{f} (hexane:TBME 4:1) = 0.22 (Mostaine). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \(\delta 1.47 (s, 9\text{H}), 2.02-2.14 (m, 3\text{H}), 2.40-2.48 (m, 3\text{H}), 3.68 (s, 1\text{H}).

**3-Hydroxy-3-acetyl-1-phenyl-2-pyrrolidinone (S16)**

Oxaziridine 63 (874 mg, 1.1 eq) was added to a mixture of 3-acetyl-1-phenyl-2-pyrrolidinone (500 mg, 2.46 mmol) and AlCl\textsubscript{3} (16 mg, 5 mol%) in 15 mL of toluene at room temperature. The mixture was stirred for 2 h and filtered. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 2:1) giving the product as a yellow solid (454 mg, 67%).

**C\textsubscript{12}H\textsubscript{13}NO\textsubscript{3} (Mr = 219.24).** R\textsubscript{f} (hexane/ethyl acetate 2:1) = 0.25 (UV, mostaine). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta 2.26 (ddd, J = 13.5, 9.8, 8.2 \text{ Hz}, 1\text{H}, \text{CH}_2), 2.35 (s, 3\text{H}, \text{CH}_3), 2.69 (ddd, J = 13.3, 7.01, 3.0 \text{ Hz}, 1\text{H}, \text{CH}_2), 3.87-4.03 (m, 2\text{H}, \text{OH}, \text{CH}_2\text{N}), 4.27 (s, 1\text{H}, \text{OH}), 7.18-7.24 (m, 1\text{H}), 7.37-7.43 (m, 2\text{H}), 7.56-7.62 (m, 2\text{H}).
3. Experimental Part

Preparation of Optically Active α-Fluoro-β-keto Esters and α-Chloro-β-keto Esters

**Ethyl 2-fluoro-2-methyl-3-oxo-3-phenylpropanoate (S1, 40% ee)**

To a solution of ethyl 2-methyl-3-oxo-3-phenylpropanoate (500 mg, 2.42 mmol) in 5 mL of CH$_3$CN, complex $R,R$-Til (99.8 mg, 0.121 mmol, 5 mol%) was added. The resulting mixture was stirred to a homogenous solution before F-TEDA (918 mg, 1.07 eq) was added portionwise. The resulting mixture was stirred overnight and 100 mL of TBME was added. The organic phase was washed with water, dried over MgSO$_4$, and evaporated under reduced pressure, and the residue was subjected to flash chromatography on silica gel (hexane: TBME 15:1) to give the product as a white solid (360 mg, 81%, 40% ee).

C$_{12}$H$_{13}$FO$_3$ (Mr = 224.23). R$_f$ (hexane:TBME 10:1) = 0.31 (UV, KMnO$_4$). $^1$H NMR (200 MHz, CDC$_1$$_3$): δ 1.20 (t, $J$ = 7.25 Hz, 3H), 1.89 (d, $J$ = 22 Hz, 3H), 4.25 (qd, $J$ = 7.25, 1.0 Hz, 2H), 7.43-7.50 (m, 2H), 7.65-7.70 (m, 1H), 8.02-8.07 (m, 2H); $^{19}$F NMR (188.13 MHz, CDC$_1$$_3$): δ -151.6 (qt, $J$ = 22, 1.7 Hz). HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6mm) OB-H, hexane:PrOH (96:4), 0.5 mL/min, detector 254 nm, retention time, 13.5 (minor) and 16.0 (major) min.

**Phenyl 2-fluoro-2-methyl-3-oxo-pentanoate (S3, 75% ee)**

To a solution of the phenyl 2-methyl-3-oxo-pentanoate (1.06 g, 4.85 mmol) in 10 mL of CH$_3$CN, complex $R,R$-Til (200 mg, 0.24 mmol, 5 mol%) was added. The resulting mixture was stirred to a homogenous solution before F-TEDA (1.84 g, 1.16 eq) was added portionwise. The resulting mixture was stirred for 10 h followed by the addition of 100 mL of TBME. The organic phase was washed with water, dried over MgSO$_4$, and evaporated under reduced pressure, and the residue was subjected to flash chromatography on silica gel (hexane: TBME 15:1) to give the product as a white solid (1g, 92%, 75% ee).

C$_{13}$H$_{15}$FO$_4$ (Mr = 254.254). R$_f$ (hexane/TBME 5:1) = 0.3 (Mostaine). $^1$H NMR (200 MHz, CDC$_1$$_3$): δ 1.15 (t, $J$ = 7.0 Hz, 3H, CH$_3$), 1.83 (d, $J$ = 22.2 Hz, 3H, CH$_3$), 2.82 (dq, $J$ = 7.3, 3.0 Hz, 2H, CH$_2$), 7.08-7.12 (m, 2H, Ar), 7.25-7.30 (m, 1H, Ar), 7.36-7.44 (m, 2H, Ar); $^{19}$F NMR (188.31 MHz, CDC$_1$$_3$): δ -159.15 (qd, $J$ = 22.2, 3.0 Hz). GC conditions: GC column ß-dex, 132 °C iso, retention time, 23.7 and 24.3 (major) min.

**(3R)-3-Acetyl-3-fluoro-1-phenyl-2-pyrrolidinone (S10, 53% ee)**

To a solution of the 3-acetyl-1-phenyl-2-pyrrolidinone (116mg, 0.57 mmol) in 5 mL of CH$_3$CN, catalyst ($S,S$)-Til (23.7 mg, 0.03 mmol) was added, and the mixture was stirred to a clear yellow solution before it was cooled to -10 °C. Then F-TEDA (234 mg, 0.66 mmol) was added portionwise. The resulting mixture was stirred for 10 h, and then quenched at 0 °C by the addition of 100 mL of TBME. The organic phase was washed with water, dried over MgSO$_4$, and evaporated under reduced pressure, and the residue was subjected to flash chromatography on silica gel (hexane: TBME 15:1) to give the product as a white solid (320 mg, 78%, 53% ee).
and evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel (hexane:TBME 3:1) to give the product as a white solid (79.4%, 53% ee).

**C₁₂H₁₂FNO₂ (M_r = 221.23).** R_f (hexane/TBME 1:1) = 0.43 (UV, KMnO₄). **¹H NMR** (200 MHz, CDCl₃): δ 2.26-2.45 (m, 1H), 2.47 (d, J_HF = 4.8 Hz, 3H, CH₃), 2.78-2.90 (m, 1H), 3.88-4.02 (m, 2H), 7.21-7.30 (m, 1H), 7.40-7.43 (m, 2H), 7.60-7.63 (m, 2H), **¹⁹F NMR** (188.3 MHz, CDCl₃): δ -157.1 to -157.4 (m). HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (96:4), 1.0 mL/min, detector 210 nm, retention time, 15.1 and 22.9 (major) min.

**Diphenylmethyl 2-chloro-3-oxo-2-methylpentanoate (S13)**

R,R-Ti (41 mg, 5 mol%) was added to a solution of diphenylmethyl 2-methyl-3-oxo-pentanoate (294.5 mg, 1 mmol) in 20 mL of acetonitrile, and the mixture was stirred for 10 min resulting in a deep red solution. Then NCS (160.2 mg, 1.16 eq) was added. The reaction mixture was stirred for 2 h (TLC) and extracted with water (50 mL) and TBME (100 mL). The organic phase was dried over MgSO₄ and evaporated. Flash chromatography on silica gel (hexane:TBME 15:1) gave the product as a colorless oil (307 mg, 94%). The two enantiomers were not separated by chiral HPLC but the value of α was measured. [α]D = -5.08 (c = 1.23, MeOH).

**C₁₉H₁₉ClO₃ (M_r = 330.81).** R_f (hexane/TBME 5:1) = 0.59 (UV, Mostain). [α]D = -5.08 (c = 1.23, MeOH). **¹H NMR** (300 MHz, CDCl₃): δ 1.01 (t, J = 7.2 Hz, 3H, CH₃CH₂), 1.86 (s, 3H, CH₃), 2.48 (dq, J = 18.3, 7.2 Hz, 1H, CH₂CH₃), 2.73 (dq, J = 18.3, 7.2 Hz, 1H, CH₂CH₃), 6.91 (s, 1H, CHPh₂), 7.26-7.38 (m, 10H, 2Ar).

**Preparation Racemic Mixture (Including α-Fluoro-β-hydroxy Esters, α-Fluoro-β-hydroxy Amide, α-Chloro-α-fluoro-β-hydroxy Esters, α-Chloro-β-hydroxy Esters, α,β-Dihydroxy Ester and α,β-Dihydroxy Amide)**

**General procedure**

NaBH₄ (1.1 eq) was added to a solution of substrate (α-fluoro-β-keto ester, α-chloro-β-keto ester or α-hydroxy-β-keto ester, etc.) in methanol at -30 °C. One drop of AcOH was added to quench the reaction after full conversion (TLC) and 100 mL of TBME was added. The organic phase was washed with saturated NaHCO₃, brine, dried over MgSO₄. After evaporation of the solvent, the residue was purified by column chromatography over silica gel eluting to give the pure product.

**Preparation of Racemic α-Fluoro-β-hydroxy Esters and α-Fluoro-β-hydroxy Amides**

Ethyl 2-fluoro-3-hydroxy-2-methyl-3-phenylpropionate (P1)
3. Experimental Part

NaBH₄ 42 mg, 1.10 mmol, 1.1 eq
Substrate 224 mg, 1 mmol
Methanol 5 mL
Purification (FC) hexane:TBME 3:1
Product 127 mg, 99%, with dr = 1:1

C₁₂H₁₅F₀₃ (Mᵣ = 226.24).

The less polar diastereoisomer (95 mg): Rₕ (hexane/TBME 2:1) = 0.33 (KMNₐ₄). ¹H NMR (200 MHz, CDCl₃): δ 1.18 (t, J = 7.2 Hz, 3H), 1.61 (d, J = 22 Hz, 3H), 2.80 (dd, J = 5.2, 1.2 Hz, OH), 4.16 (qd, J = 7.1, 1.2 Hz, 2H), 4.96 (dd, J = 15.8, 5.0 Hz, 1H), 7.42-7.30 (Ar, m, 5H); ¹³C NMR (75.5 MHz, CDCl₃): δ 14.1 (CH₃), 19.6 (d, J = 23.6 Hz, CH₃), 62.0 (CH₂O), 76.4 (d, J = 23.0 Hz, CH), 96.2 (d, J = 190.9 Hz, CF), 127.7 (CH), 127.7 (CH), 128.3 (CH), 128.7 (CH), 137.8 (C), 172.0 (d, J = 24.0 Hz, CO); ¹⁹F NMR (188.13 MHz, CDCl₃): δ -165.2 (qd, J = 22, 16 Hz).

HPLC conditions: Agilent 1100, Daicel Chiralcel Column (250 x 4.6 mm) OD-H, Hexane:PrOH (98.5:1.5), 1.0 mL/min, detector 210 nm, retention time, 23.4 and 25.9 min.

The more polar diastereoisomer (129 mg): Rₕ (hexane/TBME 2:1) = 0.36 (KMNₐ₄). ¹H NMR (200 MHz, CDCl₃): δ 1.24 (t, J = 7.2 Hz, 3H), 1.37 (d, J = 22 Hz, 3H), 2.80 (d, J = 6.4 Hz, OH), 4.16 (q, J = 7.2 Hz, 2H), 4.92 (dd, J = 21, 6.6 Hz, 1H), 7.38-7.31 (Ar, m, 5H); ¹³C NMR (75.5 MHz, CDCl₃): δ 14.2 (CH₃), 20.6 (d, J = 23.5 Hz, CH₃), 62.2 (CH₂O), 77.6 (d, J = 20.7 Hz, CH), 96.6 (d, J = 193.2 Hz, CF), 128.0 (CH), 128.0 (CH), 128.5 (CH), 128.8 (CH), 137.6 (C), 171.3 (d, J = 25.3 Hz, CO); ¹⁹F NMR (188.13 MHz, CDCl₃): δ -171.2 (pentet, J = 22 Hz).

HPLC conditions: Agilent 1100, Daicel Chiralcel Column (250 x 4.6 mm) OD-H, Hexane:PrOH (98.5:1.5), 1.0 mL/min, detector 210 nm, retention time, 31.2 and 39.9 min.

Benzyl 2-fluoro-3-hydroxy-2-methylbutanoate (P2)

NaBH₄ 43.5 mg, 1.15 mmol, 1.1 eq
Substrate 234 mg, 1.04 mmol
Methanol 5 mL
Purification (FC) hexane:TBME 5:1
Product 90.5 mg, 38.5%, with dr = 1:1

C₁₂H₁₅F₀₃ (Mᵣ = 226.24). Rₕ (hexane/TBME 2:1 = 0.34 (UV, Mostaine). IR (film, cm⁻¹): 3458 (s), 2986 (m), 1743 (s), 1456 (m), 1283 (s), 1129 (s), 1102 (s), 689 (m); Anal. Calcd for C₁₂H₁₅F₀₃: C, 63.71; H, 6.82. Found: C, 63.73; H, 6.77.

The less polar diastereomer: ¹H NMR (300 MHz, CDCl₃): δ 1.21 (dd, J = 6.6, 0.9 Hz, 3H, CH₃), 1.60 (d, J = 21.9 Hz, 3H, CH₃), 2.07 (s, OH), 4.00 (dq, J = 16.8, 6.6 Hz, 1H, CHOH), 4.68 (s, 2H, CH₂Ph), 7.27-7.38 (m, 5H, Ph); ¹³C NMR (75.5 MHz, CDCl₃): δ 17.1 (d, J = 4.8 Hz, CH₃), 19.6 (d, J = 23.9 Hz, CH₃), 56.4 (CH₂Ph), 70.9 (d, J = 23.6 Hz, CH), 96.0 (d, J = 187.3 Hz, CF), 128.4 (CH), 128.7 (CH), 128.8 (CH), 135.1 (C), 170.9 (d, J = 25.1 Hz, CO); ¹⁹F NMR (188.3 MHz, CDCl₃): δ -166.78 (dq, J = 22.0, 16.9 Hz).

The more polar diastereomer: ¹H NMR (300 MHz, CDCl₃): δ 1.32 (d, J = 6.6 Hz, 3H, CH₃), 1.54 (d, J = 21.6 Hz, 3H, CH₃), 1.91 (s, OH), 4.05 (dq, J = 18.3, 6.6 Hz, 1H, CHOH), 5.26 (s, 2H, CH₂Ph), 7.34-7.38 (m, 5H, Ph); ¹³C NMR (62.9 MHz, CDCl₃): δ 16.7 (d, J = 4.2 Hz, CH₃), 19.7 (d, J = 28.5 Hz, CH₃), 67.5 (CH₂Ph), 71.1 (d, J = 23.6 Hz, CH), 97.2 (d, J = 188.4
3. Experimental Part

Hz, CF), 128.4 (CH), 128.7 (CH), 128.8 (CH), 135.3 (C), 171.9 (d, J = 25.8 Hz, CO); ^19^F
NMR (188.3 MHz, CDCl$_3$): $\delta$ -170.65 (dq, J = 21.5, 18.6 Hz).

**Phenyl 2-fluoro-3-hydroxy-2-methylpentanoate (P3)**

NaBH$_4$ 21.3 mg, 0.56 mmol, 1.1 eq

Substrate 114.6 mg, 0.5 mmol

Methanol 5 mL

Purification (FC) hexane:TBME 3:1

Product 39 mg, 34% with dr = 1:2

C$_{12}$H$_{15}$FO$_3$ (M$_r$ = 226.24). R$_f$ (hexane/TBME 3:1) = 0.3 (KMn$_4$). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.83-0.88 (m, 3H, CH$_3$CH$_2$), 1.07-1.14 (m, 3H, CH$_3$CH$_2$), 1.42-1.87 (m, 2H, CH$_2$CH$_3$), 1.70 (d, J = 21.6 Hz, CH$_3$ major), 1.75 (d, J = 22 Hz, CH$_3$ minor), 2.02 (d, J = 6.0 Hz, OH, major), 2.09 (d, J = 6.0 Hz, OH, minor), 3.83-3.95 (m, 1H, CH$_2$OH), 7.10-7.14 (m, 2H, Ph), 7.24-7.29 (m, 1H, Ph), 7.38-7.43 (m, 2H, Ph), $^1$C NMR (62.9 MHz, CDCl$_3$): $\delta$ 10.5 (CH$_3$, major), 10.8 (CH$_3$, minor), 19.9 (J = 23.8 Hz, CH$_3$, major), 20.0 (d, J = 23.8 Hz, CH$_3$, minor), 23.8 (d, J = 3.4 Hz, CH$_2$ major), 24.6 (d, J = 3.8 Hz, CH$_2$, minor), 67.6 (d, J = 22.9 Hz, CH), 97.0 (d, J = 188.1 Hz, CF, minor), 97.2 (d, J = 188.89 Hz, CF, major), 121.4 (CH), 126.5 (CH), 129.7 (CH), 150.4 (C), 170.0 (d, J = 26.3 Hz, CO), $^1$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -165.3 (qd, J = 22.0, 17.5 Hz, minor), -169.0 (pentet, J = 13.0 Hz, major), IR (neat): 688.5, 747.8, 985.3, 1092.9, 1263.3, 1409.7, 1703.1, 2969.6, 3447.9. HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, Hexane:i-PrOH (99:1), 1.0 mL/min, detector 254 nm, retention time, 19.0, 20.1, 22.8, 24.0 min.

**4-Methoxyphenyl 2-fluoro-3-hydroxy-2-methylpentanoate (P4)**

NaBH$_4$ 21 mg, 0.28 mmol, 1.1 eq

Substrate 64 mg, 0.25 mmol

Methanol 5 mL

Purification (FC) hexane:TBME 4:1

Product 58 mg, 90% with dr = 1:1.3

C$_{13}$H$_{17}$FO$_4$ (M$_r$ = 256.270). R$_f$ (hexane/TBME 3:1) = 0.23 (UV, Mostaine).

First diastereomer (the minor one): $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.07 (t, J = 7.2 Hz, 3H, CH$_3$), 1.74 (d, J = 22.0 Hz, 3H, CH$_3$), 1.45-1.86 (m, 2H, CH$_2$CH$_3$), 2.04 (br, 1H, OH), 3.80 (s, 3H, OCH$_3$), 3.80-4.00 (m, 1H, CH), 6.88-6.93 (m, 2H, Ar), 7.01-7.07 (m, 2H, Ar); $^1$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 10.8, 20.0 (d, J = 23.8 Hz, CH$_3$), 24.6 (d, J = 4.0 Hz, CH$_2$), 55.8, 76.5 (d, J = 23.0 Hz, CHOH), 97.0 (d, J = 187.8 Hz, CF), 114.7, 122.1, 143.7, 157.8, 170.0 (d, J = 25.3 Hz, CO), $^1$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -165.4 (dq, J = 22.2, 17.5 Hz).

Second diastereomer (the major one): $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.10 (t, J = 7.2 Hz, 3H, CH$_3$), 1.70 (d, J = 21.8 Hz, 3H, CH$_3$), 1.45-1.86 (m, 2H, CH$_2$CH$_3$), 2.04 (br, 1H, OH), 3.80 (s, 3H, OCH$_3$), 3.80-4.00 (m, 1H, CH), 6.88-6.93 (m, 2H, Ar), 7.01-7.07 (m, 2H, Ar); $^1$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 10.5, 19.95 (d, J = 23.7 Hz, CH$_3$), 23.8 (d, J = 3.4 Hz, CH$_2$), 55.8, 76.7 (d, J = 23.0 Hz, CHOH), 97.2 (d, J = 188.8 Hz, CF), 114.7, 122.1, 143.7, 157.8, 170.3 (d, J = 26.5 Hz, CO), $^1$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -168.9 (heptet, J = 21.66 Hz).
3. Experimental Part

**MS** m/z (relative intensity): 256.11 (M+, 17.06), 124 (100), 41, 81, 109, 151, 170, 198, 227, 257 (M+1); **HRMS (EI)** Calcd for C_{13}H_{17}FO_{4} 256.1106. Found: 256.1106; **Anal. Calcd** for C_{13}H_{17}FO_{4}: C, 60.93; H, 6.69. Found: C, 60.89; H, 6.95; N, 0.47. **HPLC** conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, Hexane: PrOH (95:5) 0.8 mL/min, detector 254 nm, Retention time, 15.4, 17.6, 19.6 and 26.8 min.

**Diphenylmethyl 2-fluoro-3-hydroxy-2-methylpentanoate (P5)**

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<th>Mol (mmol)</th>
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Purification (FC) hexane:TBME 5:1

Product 153 mg, 76% with dr = 3:1

C_{19}H_{21}FO_{3} (Mr = 316.367). R_{f} (hexane/TBME 5:1) = 0.18, 0.21 (Mostaine). **Anal. Calcd** for C_{12}H_{15}FO_{3}: C, 72.13; H, 6.69. Found: C, 72.20; H, 6.94.

The less polar diastereomer (major): ^{1}H NMR (300 MHz, CDCl_{3}): δ 1.01 (t, J = 7.2 Hz, 3H, CH_{3}), 1.58 (d, J = 21.6 Hz, 3H, CH_{3}), 1.27-1.44 (m, 1H, CH_{2}CH_{3}), 2.00 (d, J = 8.1 Hz, 1H, OH), 1.58-1.71 (m, 1H, CH_{2}CH_{3}), 3.72-3.83 (m, 1H, CH(OH)), 6.98 (s, 1H, CHPh_{2}), 7.28-7.37 (m, 10H, 2Ar), ^{13}C NMR (75.5 MHz, CDCl_{3}): δ 10.4, 19.8 (d, J = 23.7 Hz, CH_{3}), 23.8 (d, J = 3.2 Hz, CH_{2}), 76.4 (d, J = 23.4 Hz, CH(OH)), 78.3 (CHPh_{2}), 97.0 (d, J = 188.3 Hz, CF), 127.2 (d, J = 1.13 Hz), 128.3, 128.7 (d, J = 2.5 Hz), 139.5, 170.4 (d, J = 25.4 Hz), ^{19}F NMR (188.3 MHz, CDCl_{3}): δ -166.98 (dq, J = 22.0, 16.8 Hz).

The more polar diastereomer (minor): ^{1}H NMR (300 MHz, CDCl_{3}): δ 0.95 (t, J = 7.2 Hz, 3H, CH_{3}), 1.27-1.52 (m, 2H, CH_{2}CH_{3}), 1.64 (d, J = 22.2 Hz, 3H, CH_{3}), 1.92 (brs, 1H, OH), 3.65-3.78 (m, 1H, CH(OH)), 6.96 (s, 1H, CHPh_{2}), 7.27-7.42 (m, 10H, 2Ar), ^{13}C NMR (75.5 MHz, CDCl_{3}): δ 10.6, 19.8 (d, J = 24.0 Hz, CH_{3}), 24.4 (d, J = 3.7 Hz, CH_{2}), 76.1 (d, J = 22.8 Hz, CH(OH)), 78.2 (CHPh_{2}), 96.8 (d, J = 188.1 Hz, CF), 127.2 (d, J = 18.6 Hz), 128.4 (d, J = 8.7 Hz), 128.7 (d, J = 2.5 Hz), 139.4, 170.2 (d, J = 25.1 Hz), ^{19}F NMR (188.3 MHz, CDCl_{3}): δ -167.4 (dq, J = 22.0, 17.7 Hz).

**2,4,6-Triisopropylbenzyl 2-fluoro-3-hydroxy-2-methylpentanoate (P6)**

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Purification (FC) hexane:TBME 4:1

Product 379 mg, 95% with dr = 2.7:1

C_{22}H_{35}FO_{3} (Mr = 365.510). R_{f} (hexane/TBME 3:1) = 0.31 (Mostaine). **IR** (film, cm^{-1}): 3436.3 (br), 2964.3 (s), 1739.6 (s), 1608.5 (m), 1460.5 (s), 1270.3 (s), 1103.7 (s), 943.8 (m). First diastereomer: ^{1}H NMR (300 MHz, CDCl_{3}): δ 1.02 (t, J = 7.2 Hz, 3H, CH_{3}), 1.24 (d, J = 6.9 Hz, 6H), 1.25 (d, J = 6.9 Hz, 6H), 1.26 (d, J = 6.9 Hz, 6H), 1.58 (d, J = 21.6 Hz, 3H), 1.94 (dd, J = 4.7, 1.2 Hz, OH), 2.88 (pentet, J = 6.9 Hz, 1H), 3.17 (pentet, J = 6.9 Hz, 1H), 3.37 (pentet, J = 6.9 Hz, 1H), 3.62-3.75 (m, 1H), 4.77 (d, J = 5.1 Hz), 5.32 (s, 2H, OCH_{2}Ar), 7.05 (s, 2H-Ar); ^{19}F NMR (188.3 MHz, CDCl_{3}): δ -167.3 (dq, J = 21.6, 3.6 Hz).
Second diastereomer: \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.01 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)), 1.24 (d, \(J = 6.9\) Hz, 6H), 1.25 (d, \(J = 6.9\) Hz, 6H), 1.26 (d, \(J = 6.9\) Hz, 6H), 1.54 (d, \(J = 21.6\) Hz, 3H), 1.91 (dd, \(J = 4.7, 1.2\) Hz, OH), 2.90 (pentet, \(J = 6.9\) Hz, 1H), 3.17 (pentet, \(J = 6.9\) Hz, 1H), 3.37-3.62 (m, 1H), 4.77 (d, \(J = 5.1\) Hz), 5.33 (s, 2H, OCH\(_2\)Ar), 7.05 (s, 2H-Ar). \(^{19}\)F NMR (188.3 MHz, CDCl\(_3\)): \(\delta\) -166.5 (dq, \(J = 22.2, 4.7\) Hz).

**tert-Butyl 1-fluoro-2-hydroxycyclopentanecarboxylate (P7)**

- **NaBH\(_4\)**: 30 mg, 0.79 mmol, 1.1 eq
- **Substrate**: 145 mg, 0.72 mmol
- **Methanol**: 4 mL
- **Purification (FC)**: hexane:TBME 5:1
- **Product**: 100 mg, 68% with dr = 3:1

**C\(_{10}\)H\(_{17}\)FO\(_3\) (M\(_r\) = 204.24).** Anal. Calcd for C\(_{10}\)H\(_{17}\)FO\(_3\): C, 58.81; H, 8.39. Found: C, 58.78; H, 8.50.

The less polar diastereoisomer: R\(_f\) (hexane/ethyl acetate 4:1) = 0.28 (Mostaine). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.31 (d, \(J = 7.2\) Hz, 3H, CH\(_3\)), 1.34-1.42 (m, 1H), 1.57-1.87 (m, 6H), 2.02-2.19 (m, 1H), 3.02 (bd, \(J = 2.1\) Hz, 1H, OH), 3.93 (m, 1H), 4.26 (q, \(J = 7.2\) Hz, 2H, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta\) 14.0, 20.1, 20.8 (d, \(J = 4.7\) Hz), 28.8 (d, \(J = 2.6\) Hz), 29.8 (d, \(J = 21.1\) Hz), 61.8, 70.2 (d, \(J = 25.7\) Hz), 94.7 (d, \(J = 187.3\) Hz), 171.4 (d, \(J = 24.8\) Hz, CO, ester); \(^{19}\)F NMR (188.3 MHz, CDCl\(_3\)): \(\delta\) -161.1 (b).

**Ethyl 1-fluoro-2-hydroxycyclohexanecarboxylate (P8)**

\(R,R-Ru:S,S^-S-Ru\) (1:1) 3 mg, 1 mol%

- **Substrate**: 92 mg, 0.5 mmol
- **3-propanol**: 3 mL
- **Purification (FC)**: hexane:TBME 5:1
- **Product**: 86 mg, 90% with dr > 70:1

**C\(_{9}\)H\(_{15}\)FO\(_3\) (M\(_r\) = 190.212).**

The less polar diastereomer: R\(_f\) (hexane/ethyl acetate 4:1) = 0.28 (Mostaine). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.31 (d, \(J = 7.2\) Hz, 3H, CH\(_3\)), 1.34-1.42 (m, 1H), 1.57-1.87 (m, 6H), 2.02-2.19 (m, 1H), 3.02 (bd, \(J = 2.1\) Hz, 1H, OH), 3.93 (m, 1H), 4.26 (q, \(J = 7.2\) Hz, 2H, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta\) 14.0, 20.1, 20.8 (d, \(J = 4.7\) Hz), 28.8 (d, \(J = 2.6\) Hz), 29.8 (d, \(J = 21.1\) Hz), 61.8, 70.2 (d, \(J = 25.7\) Hz), 94.7 (d, \(J = 187.3\) Hz), 171.4 (d, \(J = 24.8\) Hz, CO, ester); \(^{19}\)F NMR (188.3 MHz, CDCl\(_3\)): \(\delta\) -161.1 (b).
3-Fluoro-3-(1-hydroxyethyl)-2(3H)-furanone (P9)

NaBH₄  25 mg, 0.66 mmol, 1.1 eq
Substrate  88 mg, 0.60 mmol
Methanol  10 mL
Purification (FC) hexane:TBME 5:1
Product  63 mg, 70% with dr = 1:3

C₆H₉F₀₃ (Mr = 148.132). R₂ (hexane/ethyl acetate 2:1) = 0.25, 0.17 (Mostaine). ¹H NMR (200 MHz, CDCl₃): δ 1.37 (d, J = 6.4 Hz, 3H, CH₃), 2.00-2.77 (m, 3H), 4.20-4.53 (m, 3H); ¹⁹F NMR (188.3 MHz, CDCl₃): δ -163.2 (dt, J = 26.3, 7.8 Hz, less polar isomer, minor) and -164.8 (dt, J = 24.6, 14.7 Hz, more polar isomer, major).

3-Fluoro-3-(1-hydroxyethyl)-1-phenyl-2-pyrrolidinone (P10)

NaBH₄  35 mg, 0.9 mmol, 1.1 eq
Substrate  187 mg, 0.85 mmol
Methanol  5 mL
Purification (FC) hexane:TBME 1:1
Product  183 mg, 97%, with dr = 1:10

C₁₂H₁₄FN₀₂ (Mr = 223.24). MS m/z (relative intensity): 223 (M⁺, 12.24), 28, 45, 77, 106, 119, 160, 179 (100); Anal. Calcd for C₁₂H₁₅FO₃: C, 64.56; H, 6.32, N, 6.27. Found: C, 64.69; H, 6.35; N, 6.28.

The less polar diastereoisomer (17.5mg): R₂ (hexane/TBME 1:2) = 0.34 (UV, KMnO₄). m.p. 72-73 °C. ¹H NMR (200 MHz, CDCl₃): δ 1.31 (d, J = 7 Hz, 3H, CH₃), 2.13-2.31 (m, 1H), 2.47-2.74 (m, 2H), 3.75-4.00 (m, 2H), 4.31 (dq, J = 10 Hz, 7 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 8.2 Hz, 2H), 7.65 (d, J = 8.0 Hz), ¹³C NMR (50 MHz, CDCl₃): δ 16 (CH₃), 25 (d, J = 22 Hz, CH₂), 45 (d, J = 1Hz, CH₂), 67 (d, J = 31 Hz, CH), 99 (d, J = 184 Hz, CF), 120 (C), 126 (C), 129 (C), 139 (C), 169 (d, J = 22 Hz, CO); ¹⁹F NMR (188.3 MHz, CDCl₃): δ -159.9 to -158.3 (m);

The more polar diastereoisomer (165.8 mg): R₂ (hexane/TBME 1:2) = 0.40 (UV, KMnO₄). m.p. 88-90 °C. ¹H NMR (200 MHz, CDCl₃): δ 1.25 (d, J = 7 Hz, 3H, CH₃), 2.12-2.52 (m, 2H), 3.69-3.81 (m, 2H), 3.87-3.99 (m, 2H), 4.22 (dq, J = 16 Hz, 7 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.63 (d, J = 8.2 Hz), ¹³C NMR (50 MHz, CDCl₃): δ 16 (d, J = 6 Hz, CH₃), 25 (d, J = 22 Hz, CH₂), 45 (d, J = 1.5 Hz, CH₂), 69 (d, J = 25 Hz, CH), 98 (d, J = 184 Hz, CF), 120 (C), 126 (C), 129 (C), 139 (C), 169 (d, J = 23 Hz, CO); ¹⁹F NMR (188.3 MHz, CDCl₃): δ -163.9 to -163.4 (m);

Preparation of Racemic α-Chloro-α-fluoro-β-hydroxy Esters and α-Chloro-β-hydroxy Esters

Ethyl 2-chloro-3-hydroxy-2-methyl-3-phenylpropionate (P11)

NaBH₄  0.92 mmol, 1.1 eq
Substrate  208 mg, 0.86 mmol
3. Experimental Part

Methanol 5 mL
Purification (FC) hexane:TBME 3:1
Product 165 mg, 78.7%, with dr = 1:1

C_{12}H_{15}ClO_3 (M_r = 242.70). R_f (hexane/TBME 3:1) = 0.30 (KMnO_4).

^1H NMR (250 MHz, CDCl_3): δ 1.29 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.30 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.59 (s, 1.7H, CH_3), 1.65 (s, 1.3H, CH_3), 3.20 (s, OH), 3.22 (s, OH), 4.25 (q, J = 6.8 Hz, 2H, CH_2CH_3), 5.19 (s, CHOH), 5.21 (s, CHOH), 7.31-7.46 (m, 5H, Ph);

^13C NMR (62.9 MHz, CDCl_3): δ 14.0 (CH_3), 21.8 (CH_3), 22.8 (CH_3), 62.6 (CH_2), 62.7 (CH_2), 69.7 (C), 73.6 (C), 77.8 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 128.7 (CH), 137.3 (C), 137.7 (C), 170.6 (CO), 171.0 (CO);

Analyzed Calculated for C_{12}H_{15}ClO_3: C, 59.39; H, 6.23; Found: C, 59.25; H, 6.13. HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:1), 0.6 mL/min, detector 210 nm, retention time, 50.2, 57.6, 64.6, 81.7 min.

**Benzyl 2-chloro-3-hydroxy-2-methylbutanoate (P12)**

NaBH_4 41 mg, 1.1 mmol
Substrate 236.5 mg, 0.98 mmol
Methanol 8 mL
Purification (FC) hexane:TBME 3:1 to 2:5:1
Product 90% with dr = 1:3

C_{12}H_{15}ClO_3 (M_r = 242.699). R_f (hexane/TBME 3:1) = 0.22 (KMnO_4).
The less polar diastereomer (minor): ^1H NMR (300 MHz, CDCl_3): δ 1.20 (d, J = 6.3 Hz, CH_3), 1.71 (s, CH_3), 2.48 (d, J = 6.3 Hz, OH), 4.20-4.27 (m, 1H, 5.24 (s, CH_2), 7.37-7.38 (m, 5H, Ph);

^13C NMR (75.5 MHz, CDCl_3): δ 17.4 (CH_3), 23.0 (CH_3), 67.9 (CH_2), 74.3 (C), 71.2 (CH), 128.1, 128.5, 135.7 (C), 170.8 (COO, ester).
The more polar diastereomer (major): ^1H NMR (300 MHz, CDCl_3): δ 1.27 (d, J = 6.3 Hz, CH_3), 1.76 (s, CH_3), 2.38 (d, J = 6.0 Hz, OH), 4.20-4.27 (m, 1H, 5.24 (s, CH_2), 7.37-7.38 (m, 5H, Ph);

^13C NMR (75.5 MHz, CDCl_3): δ 17.3 (CH_3), 22.1 (CH_3), 67.8 (CH_2), 71.3 (C), 71.9 (CH), 128.0, 128.5, 135.7 (C), 170.8 (COO, ester).

**Diphenylmethyl 2-chloro-3-hydroxy-2-methylpentanoate (P13)**

NaBH_4 265.6 mg, 6.99 mmol, 1.1 eq
Substrate 2.101 g, 6.35 mmol
Methanol 8 mL
Purification (FC) hexane:TBME 5:1
Product oil, 158.6 mg, 75%, with dr = 2:1

C_{10}H_{21}ClO_3 (M_r = 332.82). R_f (hexane/TBME 3:1) = 0.41 (UV, KMnO_4).

^1H NMR (300 MHz, CDCl_3): δ 0.95 (t, J = 7.5 Hz, 3H, CH_3), 1.34 (heptet, J = 7.2 Hz, 2H, CH_2CH_3), 1.71 (s, 3H, CH_3), 2.37 (d, J = 6.0 Hz, OH), 3.94 (q, J = 6.0 Hz, 1H, CH), 6.90 (s, 1H, CHPh_2), 7.24-7.36 (m, 10H, 2Ar);

^13C NMR (75.5 MHz, CDCl_3): δ 11.0 (CH_3), 22.2 (CH_3), 24.7 (CH_2), 77.7 (CHPh_2), 78.7 (CHOH), 126.9 (CH), 127.2 (CH), 128.2 (CH), 128.6 (CH), 139.3 (C), 169.6 (CO);

^13C-^1H HMQC: 77.7 (CHPh_2), 78.7 (CHOH); MS m/z
3. Experimental Part

(relative intensity): 332.12 (M⁺, 0.43), 79, 152, 105, 165, 167 (100.00); HRMS (EI): Calcd for C₁₉H₂₁ClO₃ 332.1179, Found 332.1200. IR (neat): 3527, 2968, 1739, 1456, 1255, 1108, 744, 699.

The more polar diastereomer (minor, 14.2 mg): Rf (hexane/TBME 3:1) = 0.34 (UV, KMnO₄).

¹H NMR (300 MHz, CDCl₃): δ 0.99 (t, J = 7.2 Hz, 3H, CH₃C₂), 1.32-1.45 (m, 1H, CH₂CH₃), 1.59-1.37 (m, 1H, CH₂CH₃), 1.78(s, 3H, CH₃), 2.15 (d, J = 6.9 Hz, OH), 3.94 (q, J = 6.0 Hz, 1H, CH), 6.90 (s, 1H, CHPh₂), 7.24-7.36 (m, 10H, 2Ar); ¹³C NMR (75.5 MHz, CDCl₃): δ 11.0 (CH₃CH₂), 22.6 (CH₃), 24.4 (CH₂), 69.4 (CHPh₂), 78.9 (CHOH), 127.1 (CH), 127.2 (CH), 128.4 (CH), 128.8 (CH), 139.5 (C), 169.6 (CO); MS m/z (relative intensity): 332.12 (M⁺, 1.59), 77, 79, 167 (100.00), 183, 296, HRMS (EI): Calcd for C₁₉H₂₁ClO₃ 332.1179, Found 332.1177.

Ethyl 2-chloro-2-fluoro-3-hydroxy-3-phenylpropionate (P14)

To a solution of ethyl 2-chloro-2-fluoro-3-oxo-3-phenylpropanoate (247 mg, 1.0 mmol) in 5 mL of methanol, CeCl₃ (273.7 mg, 1.1 eq, 1.11 mmol) was added followed by NaBH₄ (42 mg, 1.10 mmol). After the mixture was stirred for 0.5 h (TLC) one drop of AcOH was added to quench the reaction and 100 mL of TBME was added. The organic phase was washed with saturated NaHCO₃, brine, and dried over MgSO₄. After evaporation of the solvent, the residue was purified by column chromatography over silica gel eluting with hexane:TBME (5:1) to give the less polar diastereomer (42 mg), the more polar diastereomer (78 mg) and a mixture of the two diastereoisomers (80 mg). The overall yield (200 mg) is 80%.

C₁₁H₁₂ClFO₃ (Mr = 246.663).

The less polar diastereoisomer (95 mg): Rf (hexane/TBME 3:1) = 0.38 (Mostaine). ¹H NMR (300 MHz, CDCl₃): δ 1.24 (t, J = 7.2 Hz, 3H, CH₃), 3.14(br, OH), 4.24 (q, J = 7.2 Hz, 2H, CH₂), 5.23 (d, J = 15.6 Hz, 1H, CH), 7.35-7.43 (m, Ar, 5H); ¹³C NMR (75.5 MHz, CDCl₃): δ 13.4 (CH₃), 63.6 (CH₂O), 76.9 (d, J = 21.4 Hz, CH), 105.8 (d, J = 268.9 Hz, CF), 128.3 (d, J = 1.8 Hz, CH), 128.5 (CH), 129.5 (CH), 134.9 (C), 165.0 (d, J = 27.0 Hz, CO); ¹⁹F NMR (188.13 MHz, CDCl₃): δ -129.57 (d, J = 15.8 Hz).

The more polar diastereoisomer: Rf (Hexane/TBME 3:1) = 0.31 (Mostaine). ¹H NMR (300 MHz, CDCl₃): δ 1.36 (t, J = 7.2 Hz, 3H, CH₃), 3.34(br, OH), 4.36 (q, J = 7.2 Hz, 2H, CH₂), 5.20 (d, J = 20.4 Hz, 1H, CH), 7.39-7.47 (Ar, m, 5H); ¹³C NMR (75.5 MHz, CDCl₃): δ 13.4 (CH₃), 63.6 (CH₂O), 77.6 (d, J = 21.3 Hz, CH), 104.2 (d, J = 264.7 Hz, CF), 128.3 (CH), 128.5 (d, J = 1.7 Hz, CH), 129.3 (CH), 135.2 (C), 165.5 (d, J = 28.8 Hz, CO); ¹⁹F NMR (188.13 MHz, CDCl₃): δ -135.51 (d, J = 20.1 Hz).

Preparation of Racemic α,β-Dihydroxy Ester and α,β-Dihydroxy Amide

3-Hydroxy-3-(1-hydroxyethyl)-1-phenyl-2-pyridinol (P16)

NaBH₄ 20 mg, 0.52 mmol, 1.1 eq
Substrate 104 mg, 0.47 mmol
Methanol 3 mL

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3. Experimental Part

Analysis (FC) hexane:TBME 2:1

Product 102 mg, 98% with dr = 2:1

The secondary purification by flash chromatography on silica gel (CH2Cl2:MeOH 50:1) separated partly the two diastereomers to give the less polar diastereomer (51 mg), the more polar diastereomer (25 mg) and a mixture of the two isomer (19 mg). The overall yield is 90% after two times purification by chromatography.

C12H15NO3 (Mr = 221.252).

The less polar diastereomer: Rf (hexane/ethyl acetate 1:2) = 0.38 (UV, Mostain). M.p. 107-110°C. 1H NMR (250 MHz, CDCl3): δ 1.14 (d, J = 6.5 Hz, 3H, CH3), 2.07 (bt, J = 6.1 Hz, 2H, CH2), 3.67-4.07 (m, 3H, CH2 and OH), 4.27(s, 1H, OH), 7.12 (t, J = 7.25 Hz, 1H, Ph), 7.31 (t, J = 7.75 Hz, 2H, Ph), 7.54 (d, J = 8.25 Hz, 2H, Ph); 13C NMR (62.9 MHz, CDCl3): δ 15.4 (3CH3), 28.1 (CH2), 45.7 (NCH2), 71 (CHOH), 77.8(CH3), 120.4 (C), 125.6 (C), 129.1 (C), 138.7 (C), 175.3 (CO); MS m/z (relative intensity): 221 (M+, 5.22), 28, 45, 77, 106, 158, 160, 177 (100), 204; HRMS (EI): Calcd for C12H15NO3 221.1052, Found 221.1049; IR (KBr): 3398 (br), 2925, 2361, 1691, 1495, 1408, 1306, 1089, 767, 691. HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:iPrOH (85:15), 0.8 mL/min, detector 254 nm, retention time, 24.1 and 31.0 min.

The more polar diastereomer: Rf (hexane/ethyl acetate 1:2) = 0.21 (UV, Mostain). M.p. 123-126°C (decomp.). 1H NMR (250 MHz, CDCl3): δ 1.22 (d, J = 6.8 Hz, 3H, CH3), 2.10 (ddd, J = 16.5, 8.3, 6.5 Hz, 1H, CH2), 2.31 (ddd, J = 17.0, 8.5, 6.0 Hz, 1H, CH2), 2.76 (bd, J = 7.5 Hz, 1H, OH), 3.54 (br, 1H, OH), 3.65-3.87 (m, 3H, CH2 and CH), 7.12 (t, J = 7.38 Hz, 1H, Ph), 7.32 (t, J = 7.90 Hz, 2H, Ph), 7.56 (d, J = 8.0 Hz, 2H, Ph); 13C NMR (62.9 MHz, CDCl3): δ 17.5 (3CH3), 27.4 (CH2), 45.5 (NCH2), 71.2 (CHOH), 79.5(CMe3), 120.3 (C), 125.6 (C), 129.1 (C), 138.8 (C), 174.6 (CO); MS m/z (relative intensity): 221 (M+, 5.22), 29, 43, 57, 77, 106, 149, 176, 177 (100), 204; HRMS (EI): Calcd for C12H15NO3 221.1052, Found 221.1045; IR (KBr): 3398 (br, s), 2925, 2361, 1691(s), 1495, 1408, 1306, 1089, 767, 691. HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) OB-H, hexane:iPrOH (90:10), 0.8 mL/min, detector 254 nm, retention time, 26.0 and 30.6 min.

Asymmetric Transfer Hydrogenation for the Preparation of α-Fluoro-β-hydroxy Esters, α-Fluoro-β-hydroxy Amides, α-Chloro-β-hydroxy Esters, α-Chloro-α-fluoro-β-hydroxy Esters, α,β-Dihydroxy Esters and α,β-Dihydroxy Amides

General Procedure

A mixture of α-fluoro-β-keto ester or α-chloro-β-keto ester and Ru((1R,2R)-p-TsNCH(C6H5)CH(C6H5)NH)(η6-p-cymene) (1 mol%, i.e. R,R-Ru) or Ru((1S, 2S)-p-TsNCH(C6H5)CH(C6H5)NH)(η6-p-cymene) (1 mol%, i.e. S,S-Ru) in isopropanol were stirred under argon at room temperature until full conversion. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel to afford the product.
Asymmetric Synthesis of α-Fluoro-β-hydroxy Esters or Amides

Ethyl 2-fluoro-3-hydroxy-2-methyl-3-phenylpropionate (P1)

**R,R-Ru**  
1.5 mg, 0.0022 mmol, 1 mol%  
Substrate 50 mg, 0.22 mmol  
Isopropanol 3 mL  
Time 18 h  
Purification (FC) hexane:TBME 3:1  
Product 47 mg, 93% with dr = 1:11 (19F NMR) (38%, 3% ee)

C_{12}H_{15}FO_3 (M_r = 226.24). R_f (hexane/TBME 5:1) = 0.17 (UV, Mostaine).

The major diastereomer: **1H NMR** (200 MHz, CDCl3): δ 1.29 (t, J = 7.2 Hz, 3H, CH₃), 1.58 (d, J = 21.6 Hz, 3H), 2.90 (br, OH), 4.27 (q, J = 7.2 Hz, 2H, CH₂), 4.93 (d, J = 21.4 Hz, 1H, CH), 7.30-7.36 (m, 5H, Ar); **19F NMR** (188.13 MHz, CDCl₃): δ -171.3 (pentet, J = 21.7 Hz).

**HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (98:2) 0.8 mL/min, detector 210 nm, retention time, 31.9 (major) and 38.8 min.

The more polar diastereoisomer: **1H NMR** (200 MHz, CDCl3): δ 1.18 (t, J = 7.0 Hz, 3H, CH₃), 1.59 (d, J = 22.2 Hz, 3H), 2.90 (br, OH), 4.13 (q, J = 7.2 Hz, 2H, CH₂), 4.93 (d, J = 21.4 Hz, 1H, CH), 7.30-7.36 (m, 5H, Ar); **19F NMR** (188.13 MHz, CDCl₃): δ -165.3 (dq, J = 22.2, 16.8 Hz).

**HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (98:2), 0.8 mL/min, detector 210nm, retention time, 24.3 and 27.3 (major) min.

Ethyl 2-fluoro-3-hydroxy-2-methyl-3-phenylpropionate (P1)

**S,S-Ru**  
1.5 mg, 0.0022 mmol, 1 mol%  
Substrate 50 mg, 0.22 mmol  
Isopropanol 3 mL  
Time 18 h  
Purification (FC) hexane:TBME 3:1  
Product an oil, 43 mg, 85% with dr = 1:2 (19F NMR) (46%, 1% ee)

C_{12}H_{15}FO_3 (M_r = 226.24). R_f (hexane/TBME 5:1) = 0.17 (UV, Mostaine).

The major diastereomer: **1H NMR** (200 MHz, CDCl₃): δ 1.30 (t, J = 7.2 Hz, 3H, CH₃), 1.39 (d, J = 21.6 Hz, 3H), 2.78 (br, OH), 4.28 (q, J = 7.2 Hz, 2H, CH₂), 4.94 (d, J = 21.2 Hz, 1H, CH), 7.37-7.40 (m, 5H, Ar); **13C NMR** (62.9 MHz, CDCl₃): δ 14.2, 20.5 (d, J = 23.5 Hz, CH₃), 62.1 (CH₂), 77.5 (d, J = 20.7 Hz, CH), 96.6 (d, J = 193.3 Hz, CF), 127.9 (CH), 128.5 (CH), 128.8 (CH), 137.6 (C), 171.3 (d, J = 25.3 Hz, CO); **19F NMR** (188.13 MHz, CDCl₃): δ -171.2 (pentet, J = 21.5 Hz).

**HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (98:2), 0.8 mL/min, detector 210 nm, retention time, 32.0 (major) and 38.8 (minor) min.

The more polar diastereoisomer: **1H NMR** (200 MHz, CDCl₃): δ 1.17 (t, J = 7.0 Hz, 3H, CH₃), 1.60 (d, J = 22.2 Hz, 3H), 2.90 (br, OH), 4.14 (q, J = 7.2 Hz, 2H, CH₂), 4.94 (d, J = 21.2 Hz, 1H, CH), 7.37-7.40 (m, 5H, Ar); **13C NMR** (62.9 MHz, CDCl₃): δ 14.0, 19.5 (d, J = 23.8 Hz, CH₃), 61.9 (CH₂), 76.3 (d, J = 20.9 Hz, CH), 96.2 (d, J = 191.2 Hz, CF), 127.6 (CH), 128.3
3. Experimental Part

\( ^1H \) NMR (200 MHz, CDCl₃): \( \delta \) 1.22 (t, \( J = 7.2 \) Hz, 3H, CH₃), 1.60 (d, \( J = 22 \) Hz, 3H, CH₃), 2.23 (OH), 3.92-4.14 (m, 1H, CH), 5.19 (s, 2H, CH₂Ph), 7.27-7.38 (m, 5H, Ph); \( ^13C \) NMR (75.5 MHz, CDCl₃): \( \delta \) 17.1 (d, \( J = 4.8 \) Hz, CH₃), 19.6 (d, \( J = 23.9 \) Hz, CH₃), 67.4 (CH₂Ph), 70.9 (d, \( J = 23.6 \) Hz, CH), 96.9 (d, \( J = 187.5 \) Hz, CF), 128.4 (CH), 128.7 (CH), 128.8 (CH), 135.1 (C), 170.8 (d, \( J = 25.0 \) Hz, CO); \( ^19F \) NMR (188.3 MHz, CDCl₃): \( \delta \) -166.78 (dq, \( J = 22.0, 16.9 \) Hz);

**Benzyl 2-fluoro-3-hydroxy-2-methylbutanoate (P2)**

\( R,R-Ru \) 1.3 mg, 0.002 mmol, 1 mol%

Substrate 47 mg, 0.21 mmol

Isopropanol 2 mL

Time 20 h

Purification (FC) hexane:TBME 4:1

Product 44.2 mg, 93% with \( dr = 1:1 \) (\( ^19F \) NMR) (94%, 96% ee)

\( \text{C}_{12}\text{H}_{15}\text{FO}_3 \) (Mᵣ = 226.24). \( R_f \) (hexane/TBME 5:1) = 0.17 (UV, Mostaine).

The less polar diastereomer: \( ^1H \) NMR (200 MHz, CDCl₃): \( \delta \) 1.22 (t, \( J = 7.2 \) Hz, 3H, CH₃), 1.53 (d, \( J = 21.8 \) Hz, 3H, CH₃), 2.23 (s, OH), 3.91-4.14 (m, 1H, CHOH), 5.25 (s, 2H, CH₂Ph), 7.34-7.36 (m, 5H, Ph); \( ^13C \) NMR (62.9 MHz, CDCl₃): \( \delta \) 16.6 (d, \( J = 4.2 \) Hz, CH₃), 19.7 (d, \( J = 23.8 \) Hz, CH₃), 67.4 (CH₂Ph), 71.1 (d, \( J = 23.6 \) Hz, CH), 97.2 (d, \( J = 188.2 \) Hz, CF), 128.3 (CH), 128.6 (CH), 128.7 (CH), 135.3 (C), 171.1 (d, \( J = 25.7 \) Hz, CO); \( ^19F \) NMR (188.3 MHz, CDCl₃): \( \delta \) -170.65 (dq, \( J = 21.5, 18.6 \) Hz);

**M S** \( m/z \) (relative intensity): 226.1 (M⁺, 3.27), 91 (100), 43, 65, 107, 162, 182; HRMS (EI): Caled for \( \text{C}_{12}\text{H}_{15}\text{FO}_3 \) 226.1000, Found 226.0999; Anal. Caled for \( \text{C}_{12}\text{H}_{15}\text{FO}_3 \): C, 63.71; H, 6.82. Found: C, 63.62; H, 6.68; IR (film, cm⁻¹): 3459.6 (s), 2986.2 (m), 1742.8 (s), 1455.8 (m), 1282.5 (s), 1128.9 (s), 1101.7 (s), 689.3 (m). HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (99:1), 0.8 mL/min, detector 210 nm, retention time, 54.3 (major), 62.0 (minor), 88.5 (major) and 98.1 min (minor).

**Benzyl 2-fluoro-3-hydroxy-2-methylbutanoate (P2)**

\( S,S-Ru \) 1.3 mg, 0.002 mmol, 1mol%

Substrate 50.5 mg, 0.21 mmol

Isopropanol 2 mL

Time 20 h

Purification (FC) hexane:TBME 4:1

Product 48.2 mg, 96% with \( dr = 1:1 \) (\( ^19F \) NMR) (93%, 93% ee)

\( \text{C}_{12}\text{H}_{15}\text{FO}_3 \) (Mᵣ = 226.24). \( R_f \) (hexane/TBME 5:1) = 0.17 (Mostaine).

The less polar diastereomer: \( ^1H \) NMR (200 MHz, CDCl₃): \( \delta \) 1.22 (t, \( J = 7.2 \) Hz, 3H, CH₃), 1.60 (d, \( J = 22 \) Hz, 3H, CH₃), 2.23 (b, OH), 3.92-4.14 (m, 1H, CH), 5.19 (s, 2H, CH₂Ph),
3. Experimental Part

7.27-7.38 (m, 5H, Ph); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 17.1 (d, $J = 4.8$ Hz, CH$_3$), 19.6 (d, $J = 23.9$ Hz, CH$_3$), 67.4 (CH$_2$Ph), 70.9 (d, $J = 23.6$ Hz, CH), 96.9 (d, $J = 187.5$ Hz, CF), 128.4 (CH), 128.7 (CH), 128.8 (CH), 135.1 (C), 170.8 (d, $J = 25.1$ Hz, CO); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -166.78 (dq, $J = 22.0$, 16.9 Hz);

The more polar diastereomer: $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.22 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.53 (d, $J = 21.8$ Hz, 3H, CH$_3$), 2.23 (s, OH), 3.91-4.14 (m, 1H, CHOH), 5.25 (s, 2H, CH$_2$Ph), 7.34-7.36 (m, 5H, Ph); $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ 16.6 (d, $J = 4.3$ Hz, CH$_3$), 19.7 (d, $J = 23.8$ Hz, CH$_3$), 67.4 (CH$_2$Ph), 71.1 (d, $J = 23.6$ Hz, CH), 97.2 (d, $J = 188.2$ Hz, CF), 128.3 (CH), 128.6 (CH), 128.7 (CH), 135.3 (C), 171.1 (d, $J = 25.7$ Hz, CO); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -170.65 (dq, $J = 21.5$, 18.6 Hz);

**MS m/z** (relative intensity): 226.1 (M$^+$, 3.05), 91 (100), 43, 65, 107, 162, 182; **HRMS (EI): Calcul** for C$_{12}$H$_{15}$F$_3$ 226.1000, Found 226.1005; **Anal. Calcul** for C$_{12}$H$_{15}$F$_3$: C, 63.71; H, 6.82. Found: C, 63.92; H, 6.82; IR (film, cm$^{-1}$): 3457 (s), 2986 (m), 1742 (s), 1456 (m), 1283 (s), 1129 (s), 1102 (s), 689 (m). **HPLC conditions**: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (99:1), 0.8 mL/min, detector 210 nm, retention time, 55.4 (minor), 61.0 (major), 88.7 (minor) and 96.0 min (major).

**Phenyl 2-fluoro-3-hydroxy-2-methylpentanoate (P3)**

$R,R$-Ru 3.0 mg, 0.005 mmol, 1 mol%  
Substrate 112 mg, 0.5 mmol  
Isopropanol 4 mL  
Time 20 h  
Purification (FC) hexane:TBME 5:1 to 3:1  
Product an oil, 75mg, 66% with dr = 1:1 ($^{19}$F NMR) (72%, 98% ee)

C$_{12}$H$_{15}$F$_3$ (Mr = 226.24). R$_f$ (hexane:TBME 3:1) = 0.3 (KMnO$_4$). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.11 (t, $J = 7.4$ Hz, 3H, CH$_3$CH$_2$), 1.70 (d, $J = 21.6$ Hz, 3H, CH$_3$), 1.75 (d, $J = 22.2$ Hz, 3H, CH$_3$), 1.40-1.95 (m, 2H, CH$_2$CH$_3$), 2.18-2.03 (m, OH), 3.88 (pd, $J = 18.8$, 2.4 Hz, 1H), 7.13 (d, $J = 8.0$, 2.4 Hz, 2H), 7.26 (t, $J = 7.0$ Hz, 1H), 7.44 (t, $J = 7.5$ Hz, 2H), $^{13}$C NMR (75.8 MHz, CDCl$_3$): $\delta$ 10.3 (CH$_3$, major), 10.7(CH$_3$, minor), 19.8 ($J = 23.7$ Hz, CH$_3$, major), 19.9 (d, $J = 23.8$ Hz, CH$_3$, minor), 23.6 (d, $J = 3.3$ Hz, CH$_2$), 76.5 (d, $J = 23.0$ Hz, CH), 97.1 (d, $J = 189.0$ Hz, CF), 121.3 (C), 126.4 (C), 129.6 (C), 150.2 (C), 169.8 (d, $J = 27.0$ Hz, CO); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -165.3 (qd, $J = 22.0$, 17.3 Hz, minor), -168.9 (pentet, $J = 21.5$, 20 Hz, major); **MS m/z** (relative intensity): 226 (M$^+$, 0.80), 29, 43, 65, 77, 94(100.00), 168, 197; **HRMS (EI): Calcul** for C$_{12}$H$_{15}$F$_3$ 226.1005, Found 226.1007; **Anal. Calcul** for C$_{12}$H$_{15}$F$_3$ (226.24): C, 63.71; H, 6.88. Found: C, 63.90; H, 6.88. IR: 3448 (OH), 2971 (s), 1774 (s), 1592, 1266 (s), 985, 747, 689. **HPLC conditions**: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:1), 1.0 mL/min, detector 254 nm, retention time, 18.8 (major), 19.8 (minor); 22.9 (minor), 23.7 (major).

**Phenyl 2-fluoro-3-hydroxy-2-methylpentanoate (P3)**

$S,S$-Ru 3 mg, 0.005 mmol, 1 mol%  
Substrate 112 mg, 0.5 mmol
3. Experimental Part

Isopropanol 2 mL
Time 20 h
Purification (FC) hexane:TBME 4:1
Product an oil, 43 mg, 38% with dr = 1:1 (19F NMR) (99%, 46% ee)

$\text{C}_{12}\text{H}_{15}\text{F}_{3} \text{(Mr = 226.24).} \ R_{f} \text{(hexane:TBME 3:1) = 0.3} \text{ (KMO}_{4}. \text{ m.p. 71-72}^\circ \text{C.} \ \text{H NMR (200 MHz, CDCl}_{3}):} \ \delta \ 1.10 \text{ (t, } J = 7.2 \text{ Hz, } 3\text{H, } CH_{2}CH_{2} \text{ major), 1.11 (t, } J = 7.2 \text{ Hz, } 3\text{H, } CH_{2}CH_{2} \text{ minor), 1.70 (d, } J = 21.6 \text{ Hz, } 3\text{H, CH}_{3}), 1.75 (d, } J = 22.2 \text{ Hz, } 3\text{H, CH}_{3}), 1.45-1.95 \text{ (m, } 2\text{H, } CH_{2}CH_{2}), 2.08 (d, } J = 9 \text{ Hz, } 1\text{H, OH), 2.15 (d, } J = 6.9 \text{ Hz, } 1\text{H, OH), 3.88-3.90 (ddd, } J = 17, 7.1 \text{ Hz, } 1\text{H, CHO}, 7.13 (d, } J = 8.1, 2\text{H, Ph), 7.27 (t, } J = 7.2 \text{ Hz, } 1\text{H, Ph), 7.41 (t, } J = 7.5 \text{ Hz, 2H, Ph); C NMR (75.5 MHz, CDCl}_{3}): \ \delta \ 10.5 \text{ (CH}_{3} \text{, major), 10.8 (CH}_{3} \text{, minor), 19.9 (d, } J = 23.8 \text{ Hz, CH}_{3} \text{, minor), 20.0 (d, } J = 23.8 \text{ Hz, CH}_{3} \text{, major), 23.8 (d, } J = 3.8 \text{ Hz, CH}_{2} \text{ minor), 24.6 (d, } J = 4.0 \text{ Hz, CH}_{2} \text{ major), 76.5 (d, } J = 22.7 \text{ Hz, CH), 97.0 (d, } J = 189.0 \text{ Hz, C), 121.4 (C), 126.5 (C), 129.7 (C), 150.2 (C), 169.9 (d, } J = 25.7 \text{ Hz, CO); F NMR (188.3 MHz, CDCl}_{3}): \ \delta \ -165.3 \text{ (qd, } J = 22.0, 17.7 \text{ Hz, major), -168.9 (pentet, } J = 21.5 \text{ Hz, minor), MS m/z (relative intensity): 43, 69, 94 (100,00), 119, 131, 168, 219; HRMS (EI): Calcd for C_{12}H_{15}FO_{3} 226.1005, Found 226.1008; Anal. Calcd for C_{12}H_{15}FO_{3}: C, 63.71; H, 6.68. Found: C, 63.94; H, 6.77. HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:1), 1.0 mL/min, detector 254 nm, retention time, 18.5 (major); 22.8 (major), 24.2 (minor) min.

4-Methoxyphenyl 2-fluoro-3-hydroxy-2-methylpentanoate (P4)

$\text{R,R-Ru} \ 1.5 \text{mg, 0.0025 mmol, 1 mol%}$
Substrate 62 mg, 0.25 mmol
Isopropanol 2.5 mL
Time 20 h
Purification (FC) hexane:TBME 3:1
Product 43 mg, 91% with dr = 1:1.1 (19F NMR) (92%, 88% ee)

$\text{C}_{13}\text{H}_{17}\text{FO}_{4} \text{(Mr = 256.270).} \ R_{f} \text{(hexane:TBME 3:1) = 0.23 (UV, Mostaine).}$
First diastereomer: $\text{H NMR (300 MHz, CDCl}_{3}): \ \delta \ 1.08 (t, } J = 7.2 \text{ Hz, } 3\text{H, CH}_{3}), 1.73 (d, } J = 22.2 \text{ Hz, } 3\text{H, CH}_{3}), 1.43-1.85 (m, } 2\text{H, } CH_{2}CH_{3}), 2.33 (br, } 1\text{H, OH), 3.79 (s, } 3\text{H, OCH}_{3}), 3.74-3.91 (m, } 1\text{H, CH}, 6.88-6.91 (m, } 2\text{H, Ar), 7.01-7.05 (m, } 2\text{H, Ar); C NMR (75.5 MHz, CDCl}_{3}): \ \delta \ 10.8, 20.9 (d, } J = 23.9 \text{ Hz, CH}_{3}), 23.6 (d, } J = 3.5 \text{ Hz, CH}_{2}), 23.6 (d, } J = 22.7 \text{ Hz, CHO), 97.0 (d, } J = 188.3 \text{ Hz, CF), 114.1, 122.2, 143.6, 157.7, 170.0 (d, } J = 25.3 \text{ Hz, CO); Second diastereomer: } \text{H NMR (300 MHz, CDCl}_{3}): \ \delta \ 1.09 (t, } J = 7.2 \text{ Hz, } 3\text{H, CH}_{3}), 1.68 (d, } J = 21.6 \text{ Hz, } 3\text{H, CH}_{3}), 1.43-1.85 (m, } 2\text{H, } CH_{2}CH_{3}), 2.33 (br, } 1\text{H, OH), 3.79 (s, } 3\text{H, OCH}_{3}), 3.74-3.91 (m, } 1\text{H, CH}, 6.88-6.91 (m, } 2\text{H, Ar), 7.01-7.05 (m, } 2\text{H, Ar); C NMR (75.5 MHz, CDCl}_{3}): \ \delta \ 10.4, 20.8 (d, } J = 23.7 \text{ Hz, CH}_{3}), 24.5 (d, } J = 4.0 \text{ Hz, CH}_{2}), 27.6 (d, } J = 23.0 \text{ Hz, CHO), 97.2 (d, } J = 188.9 \text{ Hz, CF), 114.7, 122.1, 143.8, 157.7, 170.3 (d, } J = 26.2 \text{ Hz, CO); F NMR (188.3 MHz, CDCl}_{3}): \ \delta \ -165.4 (dq, } J = 22.0, 17.7 \text{ Hz, first diastereomer), -169.0 (heptet, } J = 22.9 \text{ Hz, second diastereomer).}$
MS m/z (relative intensity): 256.11 (M+, 4.30), 124 (100), 41, 81, 109, 151, 170, 198, 227, 257 (M+1)+; HRMS (EI): Calcd for C_{13}H_{17}FO_{4} 256.1106; Found 256.1107; Anal. Calcd for
C_{13}H_{17}F_{14}: C, 60.93; H, 6.69. Found: C, 60.99; H, 6.89; IR (film, cm\(^{-1}\)): 3484 (br, s), 2970 (s), 1761 (s), 1598 (m), 1507 (s), 1248 (s), 1193 (s), 1100 (s), 814 (m), 524 (s). **HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (95:5) 0.8 mL/min, detector 254 nm, retention time, 15.4, 17.6 (major), 19.6 and 26.9 (major) min.

4-Methoxyphenyl 2-fluoro-3-hydroxy-2-methylpentanoate (P4)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Isopropanol</th>
<th>Time</th>
<th>Purification (FC)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg, 0.0025 mmol, 1 mol%</td>
<td>62 mg, 0.25 mmol</td>
<td>20 h</td>
<td>hexane:TBME 5:1 to 4:1</td>
<td>61.3 mg, 95% with dr = 1:1.1 ((^{19})F NMR) (93%, 88% ee)</td>
</tr>
</tbody>
</table>

**C_{13}H_{17}F_{14} (M_r = 256.270).** \(R_f\) (hexane/TBME 3:1) = 0.23 (UV, Mostaine).

First diastereoisomer: \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.08 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)), 1.73 (d, \(J = 22.2\) Hz, 3H, CH\(_3\)), 1.45-1.85 (m, 2H, \(CH_2CH_3\)), 2.33 (br, 1H, OH), 3.79 (s, 3H, OCH\(_3\)), 3.74-3.91 (m, 1H, CH), 6.87-6.91 (m, 2H, Ar), 7.01-7.05 (m, 2H, Ar); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta\) 10.7, 19.9 (d, \(J = 23.9\) Hz, CH\(_2\)), 23.6 (d, \(J = 3.5\) Hz, CH\(_2\)), 76.4 (d, \(J = 22.7\) Hz, CHO), 97.0 (d, \(J = 188.3\) Hz, CF), 114.1, 122.2, 143.6, 157.7, 170.0 (d, \(J = 25.4\) Hz, CO).

Second diastereoisomer: \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.09 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)), 1.68 (d, \(J = 21.6\) Hz, 3H, CH\(_3\)), 1.45-1.85 (m, 2H, \(CH_2CH_3\)), 2.33 (br, 1H, OH), 3.79 (s, 3H, OCH\(_3\)), 3.74-3.91 (m, 1H, CH), 6.87-6.91 (m, 2H, Ar), 7.01-7.05 (m, 2H, Ar); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta\) 10.4, 19.8 (d, \(J = 23.7\) Hz, CH\(_3\)), 24.5 (d, \(J = 4.0\) Hz, CH\(_2\)), 76.5 (d, \(J = 23.0\) Hz, CHO), 97.2 (d, \(J = 188.9\) Hz, CF), 114.7, 122.1, 143.8, 157.7, 170.3 (d, \(J = 26.3\) Hz, CO).

**\(^{19}\)F NMR (188.3 MHz, CDCl\(_3\)): \(\delta\) -165.4 (dq, \(J = 22.0, 17.7\) Hz, first diastereoisomer), -169.0 (heptet, \(J = 22.9\) Hz, second diastereomer); MS m/z (relative intensity): 256.11 (M\(^+\), 4.26), 124 (100), 41, 81, 109, 142, 170, 198, 227, 257 (M+1) \(^{1}\); HRMS (EI): *Calcd* for C\(_{13}\)H\(_{17}\)F\(_{14}\) 256.1106, Found 256.1107, Anal. *Calcd* for C\(_{13}\)H\(_{17}\)F\(_{14}\): C, 60.93; H, 6.89; Found: C, 60.89; H, 6.81; IR (film, cm\(^{-1}\)): 3490 (br, s), 2970 (s), 1761 (s), 1598 (m), 1507 (s), 1248 (s), 1193 (s), 1100 (s), 814 (m), 524 (s). **HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (95:5) 0.8 mL/min, detector 254 nm, retention time, 15.4 (major), 17.6, 19.6 (major) and 26.9 min.

Diphenylmethyl 2-fluoro-3-hydroxy-2-methylpentanoate (P5)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Isopropanol</th>
<th>Time</th>
<th>Purification (FC)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg, 0.0025 mmol, 1 mol%</td>
<td>74 mg, 0.25 mmol</td>
<td>20 h</td>
<td>hexane:TBME 5:1</td>
<td>60 mg, 81% with dr = 1:1 ((^{19})F NMR)</td>
</tr>
</tbody>
</table>

**C_{19}H_{21}F_{3} (M_r = 316.367).** \(R_f\) (hexane/TBME 5:1) = 0.18, 0.21 (Mostaine).
3. Experimental Part

The less polar diastereoisomer: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.01 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.58 (d, $J = 21.6$ Hz, 3H, CH$_3$), 1.27-1.51 (m, 2H, $CH_2CH_3$), 2.11 (br, 1H, OH), 3.71-3.83 (m, 1H, $CHOH$), 6.98 (s, 1H, CHPh$_2$), 7.31-7.37 (m, 10H, 2Ar); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 10.4, 19.7 (d, $J = 23.8$ Hz, CH$_3$), 23.7 (d, $J = 3.2$ Hz, CH$_2$), 76.4 (d, $J = 23.5$ Hz, CHOH), 78.3 (CHPh$_2$), 97.0 (d, $J = 188.1$ Hz, CF), 127.2, 128.3, 128.7 139.5, 170.4 (d, $J = 26.3$ Hz); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -166.98 (dq, $J = 21.8$, 17.3 Hz). HPLC conditions: no good separation conditions for the less polar diastereoisomer could be found.

The more polar diastereoisomer: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.93 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.27-1.52 (m, 2H, $CH_2CH_3$), 1.65 (d, $J = 22.2$ Hz, 3H, CH$_3$), 2.11 (brs, 1H, OH), 3.71-3.83 (m, 1H, $CHOH$), 6.98 (s, 1H, CHPh$_2$), 7.31-7.37 (m, 10H, 2Ar); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 10.6, 19.8 (d, $J = 23.8$ Hz, CH$_3$), 24.4 (d, $J = 3.7$ Hz, CH$_2$), 76.1 (d, $J = 23.6$ Hz, CHOH), 78.2 (CHPh$_2$), 96.8 (d, $J = 188.2$ Hz, CF), 127.2, 128.3, 128.7 139.5, 170.2 (d, $J = 25.1$ Hz); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -167.4 (dq, $J = 21.8$, 18.1 Hz). HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane:PrOH (98:2) 0.7 mL/min, detector 210 nm, retention time, 28.4 (minor), 31.3 (major) min.

MS m/z (relative intensity): 316.15 (M$^+$, 1.43), 167 (100), 43, 77, 105, 152, 183, 210, 240, 278, 317. HRMS (EI): Calcd for C$_{19}$H$_{21}$F$_2$O$_3$: 316.1470. Found 316.1468; Anal. Calcd for C$_{19}$H$_{21}$F$_2$O$_3$: C, 72.13; H, 6.69. Found: C, 72.28; H, 6.79; IR (film, cm$^{-1}$): 3436 (s), 2973 (m), 1743 (s), 1455 (m), 1265 (s), 1105 (s), 986 (m), 743 (m), 699 (s).

Diphenylmethyl 2-fluoro-3-hydroxy-2-methylpentanoate (P5)

S,S-Ru 1.5 mg, 0.0025 mmol, 1 mol%
Substrate 77 mg, 0.25 mmol
Isopropanol 2.5 mL
Time 20 h
Purification (FC) hexane:TBME 5:1
Product 74.5 mg, 96% with dr = 1:1 ($^{19}$F NMR)

C$_{19}$H$_{22}$F$_3$O$_3$ (M$^+$ = 316.367). R$_f$ (hexane:TBME 5:1) = 0.18, 0.21 (Mostaine).

The less polar diastereoisomer: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.01 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.58 (d, $J = 21.9$ Hz, 3H, CH$_3$), 1.27-1.51 (m, 2H, $CH_2CH_3$), 2.09 (br, 1H, OH), 3.71-3.83 (m, 1H, $CHOH$), 6.98 (s, 1H, CHPh$_2$), 7.31-7.37 (m, 10H, 2Ar); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 10.4, 19.7 (d, $J = 23.8$ Hz, CH$_3$), 23.7 (d, $J = 3.2$ Hz, CH$_2$), 76.4 (d, $J = 23.5$ Hz, CHOH), 78.3 (CHPh$_2$), 97.0 (d, $J = 188.1$ Hz, CF), 127.2, 128.3, 128.7 139.5, 170.4 (d, $J = 26.3$ Hz); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -166.91 (pentet, $J = 22.1$ Hz). HPLC conditions: no good separation conditions for the less polar diastereoisomer could be found.

The more polar diastereoisomer: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.93 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.27-1.52 (m, 2H, $CH_2CH_3$), 1.65 (d, $J = 22.2$ Hz, 3H, CH$_3$), 2.09 (brs, 1H, OH), 3.71-3.83 (m, 1H, $CHOH$), 6.98 (s, 1H, CHPh$_2$), 7.31-7.37 (m, 10H, 2Ar); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 10.6, 19.8 (d, $J = 23.8$ Hz, CH$_3$), 24.4 (d, $J = 3.7$ Hz, CH$_2$), 76.1 (d, $J = 23.6$ Hz, CHOH), 78.2 (CHPh$_2$), 96.8 (d, $J = 188.2$ Hz, CF), 127.2, 128.3, 128.7 139.5, 170.2 (d, $J = 25.1$ Hz); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -167.5 (pentet, $J = 21.7$ Hz). HPLC conditions: Agilent
3. Experimental Part

1100, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane:PrOH (98:2) 0.7 mL/min, detector 210 nm, retention time, 28.8 (major), 31.2 (minor) min.

**MS m/z** (relative intensity): 316.15 (M+, 2.59), 167 (100), 43, 73, 105, 135, 152, 183, 220, 240, 295, 317; **HRMS (EI): Calculd for** C19H21FO3 316.1470, Found 316.1472; **Anal. Calculd for** C19H21FO3: C, 72.13; H, 6.69. Found: C, 72.15; H, 6.78; **IR (film, cm⁻¹):** 3436.1 (s), 2973.7 (m), 1744.0 (s), 1455.5 (m), 1265.5 (s), 985.8 (m), 744.0 (m), 699.3 (s).

2,4,6-Triisopropylbenzyl 2-fluoro-3-hydroxy-2-methylpentanoate (P6)

**R,R-Ru** 1.3 mg, 0.002 mmol, 1 mol%

Substrate 89.8 mg, 0.21 mmol

Isopropanol 2.5 mL

Time 20 h

Purification (FC) hexane:TBME 10:1

Product 86.4 mg, 96% with dr = 1:2 \((^{19}F \text{ NMR})\)

C22H35FO3 \((M_r = 365.510)\). Rf (hexane:TBME 3:1) = 0.31 (Mostaine).

First diastereoisomer: \(^1H \text{NMR} \ (300 \text{ MHz, } \text{CDCl}_3): \delta 1.02 (t, J = 7.2 \text{ Hz, } 3 \text{H, } \text{CH}_3), 1.24-1.28 \text{ (m, 18H, } 3 \text{Me}_2 \text{CH}, \ 1.59 \text{ (d, } J = 21.9 \text{ Hz, MeCF}), 1.35-1.75 \text{ (m, } CH_2CH_3, 2 \text{H}), 1.94 \text{ (s, } \text{OH}), 2.90 \text{ (pentet, } J = 6.9 \text{ Hz, } 1 \text{CHMe}_2), 3.12-3.23 \text{ (m, } 2 \text{CHMe}_2), 3.64-3.74 \text{ (m, } \text{CHOH}), 5.33 \text{ (s, OCH}_2\text{Ar}), 7.05 \text{ (s, } 2 \text{H-Ar}); \ ^{13}C \text{NMR} \ (75.5 \text{ MHz, CDCl}_3): \delta 10.7, 19.9 \text{ (d, } J = 24 \text{ Hz), 23.7 (CH}_2), 23.9, 24.1, 24.4, 24.5, 27.1, 29.7, 34.5, 60.8 \text{ (CH}_2), 76.0, 76.3, 76.6, 96.8 \text{ (d, } J = 187.1 \text{ Hz), 121.4, 125.5, 125.7, 149.1, 150.1, 171.3 \text{ (d, } J = 25.1 \text{ Hz), } ^{19}F \text{ NMR} \ (188.3 \text{ MHz, CDCl}_3): \delta -166.328 \text{ to } -166.588 \text{ (m)};**

Second diastereomer: \(^1H \text{NMR} \ (300 \text{ MHz, CDCl}_3): \delta 1.03 (t, J = 7.2 \text{ Hz, } 3 \text{H, } \text{CH}_3), 1.24-1.28 \text{ (m, 18H, } 3 \text{Me}_2 \text{CH}, \ 1.54 \text{ (d, } J = 21.9 \text{ Hz, MeCF}), 1.35-1.75 \text{ (m, } CH_2CH_3, 2 \text{H}), 1.94 \text{ (s, } \text{OH}), 2.90 \text{ (pentet, } J = 6.9 \text{ Hz, } 1 \text{CHMe}_2), 3.12-3.23 \text{ (m, } 2 \text{CHMe}_2), 3.64-3.74 \text{ (m, } \text{CHOH}), 5.34 \text{ (s, OCH}_2\text{Ar}), 7.05 \text{ (s, } 2 \text{H-Ar}); \ ^{13}C \text{NMR} \ (75.5 \text{ MHz, CDCl}_3): \delta 10.4, 19.8 \text{ (d, } J = 23.9 \text{ Hz), 23.7 (CH}_2), 23.9, 24.1, 24.4, 24.5, 27.1, 29.7, 34.5, 60.8 \text{ (CH}_2), 76.0, 76.3, 76.6, 97.0 \text{ (d, } J = 187.5 \text{ Hz), 121.4, 125.5, 125.7, 149.1, 150.1, 171.5 \text{ (d, } J = 25.6 \text{ Hz), } ^{19}F \text{ NMR} \ (188.3 \text{ MHz, CDCl}_3): \delta -167.117 \text{ to } -167.588 \text{ (m)};**

**MS m/z** (relative intensity): 366.3 (M⁺, 0.20), 216 (100), 43, 91, 106, 173, 201, 218, 250, 323, 351; **HRMS (EI): Calculd for** C22H35FO3 366.2565, Found 366.2563; **Anal. Calculd for** C22H35FO3: C, 72.49; H, 9.13. Found: C, 72.40; H, 9.41; **IR (film, cm⁻¹):** 3459 (br), 2963 (s), 1738 (s), 1608 (m), 1461 (s), 1274 (s), 1104 (s), 934 (m).

2,4,6-Triisopropylbenzyl 2-fluoro-3-hydroxy-2-methylpentanoate (P6)

**S,S-Ru** 1.3 mg, 0.002 mmol, 1 mol%

Substrate 91 mg, 0.21 mmol

Isopropanol 2.5 mL

Time 20 h

Purification (FC) hexane:TBME 10:1

Product 88.5 mg, 97% with dr = 2:1 \((^{19}F \text{ NMR})\)

C22H35FO3 \((M_r = 365.510)\). Rf (hexane/TBME 3:1) = 0.31 (Mostaine).
First diastereoisomer: $^1$H NMR (200 MHz, CDCl$_3$): δ 1.02 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.25 (d, $J = 6.8$ Hz, 18H, 3Me$_2$CH), 1.59 (d, $J = 22.2$ Hz, MeCF), 1.34-1.77 (m, 2H, CH$_2$CH$_3$), 2.01 (s, OH), 2.87-2.97 (m, 1H, CHMe$_2$), 3.10-3.25 (m, 2 CHMe$_2$), 3.60-3.79 (m, CHOCH), 5.33 (s, OCH$_2$Ar), 7.06 (s, 2H-Ar); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 10.5, 19.7 (d, $J = 24$ Hz, 23.7 (CH$_2$), 23.9, 24.2, 24.3, 24.4, 27.0, 29.5, 34.4, 60.7 (CH$_2$), 75.8, 76.1, 76.4, 96.7 (d, $J = 187.2$ Hz), 121.3, 125.5, 124.7, 125.4, 149.0, 150.0, 171.2 (d, $J = 25.1$ Hz); $^{19}$F NMR (188.3 MHz, CDCl$_3$): δ -166.81 to -166.366 (m); MS m/z (relative intensity): 366.3 (M$^+$, 0.28), 216 (100), 43, 91, 106, 173, 201, 217, 250, 323, 351; HRMS (EI): Calculated for C$_{22}$H$_{35}$FO$_3$ 366.2565, Found 366.2568; Anal. Calculated for C$_{22}$H$_{35}$FO$_3$: C, 72.49; H, 9.13. Found: C, 72.30; H, 9.64; IR (film, cm$^{-1}$): 3496 (s), 2963.8 (s), 1738 (s), 1461 (m), 1275 (s), 1175 (s), 1104 (s), 949 (m).

Second diastereoisomer: $^1$H NMR (200 MHz, CDCl$_3$): δ 1.03 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.27 (d, $J = 6.8$ Hz, 18H, 3Me$_2$CH), 1.54 (d, $J = 21.8$ Hz, MeCF), 1.34-1.77 (m, 2H, CH$_2$CH$_3$), 2.05 (s, OH), 2.87-2.97 (m, 1H, CHMe$_2$), 3.10-3.25 (m, 2 CHMe$_2$), 3.60-3.79 (m, CHOCH), 5.34 (s, OCH$_2$Ar), 7.06 (s, 2H-Ar); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 10.3, 19.7 (d, $J = 24$ Hz, 23.7 (CH$_2$), 23.9, 24.2, 24.3, 24.4, 27.0, 29.5, 34.4, 60.7 (CH$_2$), 75.8, 76.1, 76.4, 96.9 (d, $J = 187.6$ Hz), 121.3, 125.5, 124.7, 125.4, 149.0, 150.0, 171.4 (d, $J = 25.6$ Hz); $^{19}$F NMR (188.3 MHz, CDCl$_3$): δ -167.5 to -167.0 (m); MS m/z (relative intensity): 366.3 (M$^+$, 0.28), 216 (100), 43, 91, 106, 173, 201, 217, 250, 323, 351; HRMS (EI): Calculated for C$_{22}$H$_{35}$FO$_3$ 366.2565, Found 366.2568; Anal. Calculated for C$_{22}$H$_{35}$FO$_3$: C, 72.49; H, 9.13. Found: C, 72.30; H, 9.64; IR (film, cm$^{-1}$): 3496 (s), 2963.8 (s), 1738 (s), 1461 (m), 1275 (s), 1175 (s), 1104 (s), 949 (m).

**tert-Butyl 1-fluoro-2-hydroxycyclopentanecarboxylate (P7)**

- **R,R-Ru** 3 mg, 0.005 mmol, 1 mol% Substrate 100 mg, 0.5 mmol Isopropanol 3 mL Time 8 h Purification (FC) hexane:TBME 4:1 Product 80.4 mg, 80% with dr = 2:1 ($^{19}$F NMR) (46%, 100% ee). 

C$_{10}$H$_{17}$FO$_3$ (M$_r$ = 204.24).

The less polar diastereoisomer (57.3 mg): R$_f$ (hexane/TBME 5:1) = 0.22 (Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): δ 1.52 (s, 9H, CH$_3$), 1.70-2.35 (m, 6H), 2.96 (d, $J = 3.6$ Hz, 1H, OH), 4.25-4.33 (dm, $J = 13.8$ Hz, 1H, CHOCH), $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 20.6 (CH$_2$), 28.0 (CH$_3$), 32.5 (d, $J = 1.6$ Hz), 33.4 (d, $J = 23.0$ Hz), 78.5 (d, $J = 29.5$ Hz), 83.3 (s, C), 102.3 (d, $J_{C,F} = 191.5$ Hz, CF), 170.1 (d, $J = 24.7$ Hz, CO, ester); $^{19}$F NMR (188.3 MHz, CDCl$_3$): δ -156.0 (ddd, $J = 37.1, 23.7, 14.3$ Hz). HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane:$^3$PrOH (98:2), 0.8 mL/min, detector 210 nm, retention time, 9.5 (minor) and 10.6 (major) min.

The more polar diastereoisomer (20.7 mg): R$_f$ (hexane/TBME 5:1) = 0.13 (Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): δ 1.51 (s, 9H, CH$_3$), 1.61-2.31 (m, 6H), 4.25-4.37 (m, 1H, CH); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 19.1 (CH$_3$), 28.0 (CH$_3$), 31.6 (CH$_2$), 33.5 (d, $J = 22.2$ Hz, CH$_2$), 77.7 (d, $J = 19.7$ Hz, CH), 82.7 (s, C), 100.2 (d, $J = 192.1$ Hz, CF), 169.6 (d, $J = 27.5$ Hz, CO, ester); $^{19}$F NMR (188.3 MHz, CDCl$_3$): δ -174.2 (dt, $J = 30.0, 18.6$ Hz). HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane:$^3$PrOH (98:2), 0.8 mL/min, detector 210 nm, retention time, 17.3 (major) min.
3. Experimental Part

**MS** m/z (ESI): 205 (M+1)^+, 149, 171; **Anal. Calcd** for C_{10}H_{17}FO_{3}: C, 58.81; H, 8.39. Found: C, 58.64; H, 8.41.

**tert-Butyl 1-fluoro-2-hydroxycyclopentanecarboxylate (P7)**

| **S,S-Ru** | 3 mg, 0.005 mmol, 1 mol% |
| **Substrate** | 100 mg, 0.5 mmol |
| **Isopropanol** | 3 mL |
| **Time** | 8 h |
| **Purification (FC)** | hexane:TBME 4:1 |
| **Product** | 91 mg, 91% with dr = 2:1 (19F NMR) (46%, 100% ee) |

C_{10}H_{17}FO_{3} (M_r = 204.24).

The less polar diastereoisomer (60.2 mg): R_t (hexane/TBME 5:1) = 0.22 (Mostaine). \[^1\text{H} NMR (300 MHz, CDCl}_3\): \(\delta\) 1.51 (s, 9H, CH_3), 1.69-2.38 (m, 6H), 3.03 (b, 1H, OH), 4.24-4.31 (m, 1H, C\_OH); \[^{13}\text{C} NMR (75.5 MHz, CDCl}_3\): \(\delta\) 20.5 (CH_3), 28.0 (CH_3), 32.5 (d, J = 1.7 Hz), 33.4 (d, J = 23.0 Hz), 78.5 (d, J = 29.5 Hz), 83.3 (s, C), 102.3 (d, J\_CF = 191.3 Hz, CF), 170.1 (d, J = 24.3 Hz, CO, ester); \[^{19}\text{F} NMR (188.3 MHz, CDCl}_3\): \(\delta\) -156.0 (ddd, J = 36.5, 23.4, 14.3 Hz). **HPLC conditions**: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane:\text{PrOH} (98:2), 0.8 mL/min, detector 210 nm, retention time, 9.4 (major) and 10.8 (minor) min.

The more polar diastereoisomer (30.8 mg): R_t (hexane/TBME 5:1) = 0.13 (Mostaine). \[^1\text{H} NMR (300 MHz, CDCl}_3\): \(\delta\) 1.50 (s, 9H, CH_3), 1.68-2.30 (m, 6H), 4.25-4.37 (m, 1H, CH); \[^{13}\text{C} NMR (75.5 MHz, CDCl}_3\): \(\delta\) 19.1 (CH_3), 28.0 (CH_3), 31.6 (CH_2), 33.5 (d, J = 22.2 Hz, CH_2), 77.7 (d, J = 19.7 Hz, CH), 82.7 (s, C), 100.2 (d, J = 192.1 Hz, CF), 169.6 (d, J = 27.5 Hz, CO, ester); \[^{19}\text{F} NMR (188.3 MHz, CDCl}_3\): \(\delta\) -174.2 (dt, J = 30.0, 18.6 Hz). **HPLC conditions**: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane:\text{PrOH} (98:2), 0.8 mL/min, detector 210 nm, retention time, 14.5 (major) min.

**MS** m/z (ESI): 205 (M+1)^+, 149, 171; **Anal. Calcd** for C_{10}H_{17}FO_{3}: C, 58.81; H, 8.39. Found: C, 58.66; H, 8.45.

**Ethyl 1-fluoro-2-hydroxycyclohexanecarboxylate (P8)**

| **R,R-Ru** | 3.0 mg, 0.005 mmol, 1 mol% |
| **Substrate** | 91.5 mg, 0.5 mmol |
| **Isopropanol** | 3 mL |
| **Time** | 18 h |
| **Purification (FC)** | hexane:EtoAc 4:1 |
| **Product** | 78.9 mg, 83% with dr = 1:1 (19F NMR) (87%, 100% ee) |

C_{9}H_{15}F_{3}O_{3} (M_r = 190.212).

The less polar diastereoisomer: R_t (hexane/ethyl acetate 4:1) = 0.28 (Mostaine). \[^1\text{H} NMR (300 MHz, CDCl}_3\): \(\delta\) 1.32 (d, J = 7.2 Hz, 3H, CH_3), 1.25-1.45 (m, 1H), 1.58-1.91 (m, 6H), 2.02-2.21 (m, 1H), 3.00 (b, 1H, OH), 3.92-3.98 (m, 1H), 4.27 (q, J = 7.2 Hz, 2H, CH_2CH_3); \[^{13}\text{C} NMR (75.5 MHz, CDCl}_3\): \(\delta\) 14.0, 20.1, 20.8 (d, J = 4.6 Hz), 28.8 (d, J = 2.6 Hz), 29.8 (d, J = 21.1 Hz), 61.8, 70.2 (d, J = 26.1 Hz), 94.7 (d, J = 187.4 Hz), 171.5 (d, J = 24.5 Hz, CO,
ester; $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -161.28 (b); Anal. Calcd for C$_9$H$_{15}$F$_3$: C, 65.83; H, 7.95. Found: C, 57.00; H, 7.85. HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane-$^3$PrOH (90:10), 0.6 mL/min, detector 210 nm, retention time, 10.7 (minor), 13.6 (major) min.

The more polar diastereoisomer: R$_f$ (hexane/ethyl acetate 4:1) = 0.17 (Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.31 (d, $J = 7.2$ Hz, 3H, CH$_3$), 1.24-2.12 (m, 8H), 3.87-3.95 (m, 1H), 4.26 (q, $J = 7.2$ Hz, 2H, CH$_2$CH$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.1, 19.7 (d, $J = 1.3$ Hz), 23.6, 30.1 (d, $J = 2.0$ Hz), 32.3 (d, $J = 22.3$ Hz), 61.7, 71.9 (d, $J = 20.9$ Hz), 96.3 (d, $J = 189.4$ Hz), 170.9 (d, $J = 26.2$ Hz, CO, ester); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -186.34 (bt, $J = 27.7$ Hz); Anal. Calcd for C$_9$H$_{15}$F$_3$: C, 65.83; H, 7.95. Found: C, 56.90; H, 8.01. HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane-$^3$PrOH (90:10), 0.6 mL/min, detector 210 nm, retention time, 16.8 (major).

MS $m/z$ (relative intensity): 190 (M$^+$, 0.75), 18 (100.00), 28, 57, 91, 101, 126, 152, 162; HRMS (EI): Calcd for C$_9$H$_{15}$F$_3$ 190.1005, Found 190.1010.

**Ethyl 1-fluoro-2-hydroxy-cyclohexanecarboxylate (P8)**

```
\begin{center}
\includegraphics[width=0.8\textwidth]{ethy1-fluoro-2-hydroxy-cyclohexanecarboxylate.png}
\end{center}
```

$S,S$-Ru 3.0 mg, 0.005 mmol, 1 mol%

Substrate 90 mg, 0.5 mmol

Isopropanol 3 mL

Time 18 h

Purification (FC) hexane:EtOAc 4:1

Product 74 mg, 81% with dr = 1:1 ($^{19}$F NMR) (85%, 100% ee)

C$_9$H$_{15}$F$_3$ (M$_r$ = 190.212).

The less polar diastereoisomer: R$_f$ (hexane/ethyl acetate 4:1) = 0.28 (Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.32 (d, $J = 7.2$ Hz, 3H, CH$_3$), 1.24-1.45 (m, 8H), 1.58-1.89 (m, 6H), 2.01-2.20 (m, 1H), 3.01 (b, 1H, OH), 3.91-3.97 (m, 1H), 4.26 (q, $J = 7.2$ Hz, 2H, CH$_2$CH$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.0, 20.1, 20.8 (d, $J = 4.6$ Hz), 28.8 (d, $J = 2.6$ Hz), 29.8 (d, $J = 21.0$ Hz), 61.8, 70.2 (d, $J = 25.8$ Hz), 94.7 (d, $J = 187.2$ Hz), 171.4 (d, $J = 24.5$ Hz, CO, ester); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -161.2 (b); Anal. Calcd for C$_9$H$_{15}$F$_3$: C, 65.83; H, 7.95. Found: C, 57.10; H, 8.05. HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane-$^3$PrOH (90:10), 0.6 mL/min, detector 210 nm, retention time, 10.3 (major), 14.6 (minor) min.

The more polar diastereoisomer: R$_f$ (hexane/ethyl acetate 4:1) = 0.17 (Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.30 (d, $J = 7.2$ Hz, 3H, CH$_3$), 1.24-1.45 (m, 8H), 1.46-2.09 (m, 7H), 3.85-3.94 (m, 1H), 4.26 (q, $J = 7.2$ Hz, 2H, CH$_2$CH$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.1, 19.7 (d, $J = 1.4$ Hz), 23.6, 30.0 (d, $J = 2.0$ Hz), 32.3 (d, $J = 22.3$ Hz), 61.7, 71.9 (d, $J = 21.0$ Hz), 96.3 (d, $J = 189.3$ Hz), 170.9 (d, $J = 26.0$ Hz, CO, ester); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -186.33 (bt, $J = 27.7$ Hz); Anal. Calcd for C$_9$H$_{15}$F$_3$: C, 65.83; H, 7.95. Found: C, 56.82; H, 8.22. HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane-$^3$PrOH (90:10), 0.6 mL/min, detector 210 nm, retention time, 20.5 (major) min.

MS $m/z$ (relative intensity): 190 (M$^+$, 0.75), 18 (100.00), 29, 57, 91, 99, 119, 152, 162, 172; HRMS (EI): Calcd for C$_9$H$_{15}$F$_3$ 190.1005, Found 190.1080.
2-Fluoro-2-(1-hydroxyethyl)butyrolactone or 3-Fluoro-3-(1-hydroxyethyl)-2(3H)-furanone (P9)

**R,R-Ru**

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<thead>
<tr>
<th>Component</th>
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<th>Unit</th>
</tr>
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<tr>
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<td>Substrate</td>
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<td>Time</td>
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<tr>
<td>Purification (FC)</td>
<td>hexane:EtOAc 2:1</td>
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</tr>
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</table>

Product: 63 mg, 85% with dr = 1:1 ($^{19}$F NMR) (96%, 87% ee)

$C_6H_9FO_3$ (Mr = 148.132).

The less polar diastereoisomer: Rf (hexane/ethyl acetate 2:1) = 0.25 (Mostaine). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.38 (d, $J$ = 6.4 Hz, 3H, CH$_3$), 2.49 (d, $J$ = 5.2 Hz, 1H, OH), 2.28-2.54 (m, 1H), 4.27-4.38 (m, 1H), 4.40-4.56 (m, 2H); $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ 16.8, 28.2 (d, $J$ = 21.9 Hz), 65.9 (d, $J$ = 1.9 Hz), 66.5 (d, $J$ = 30.0 Hz), 95.4 (d, $J$ = 187.0 Hz), 172.5 (d, $J$ = 22.8 Hz, CO, ester); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -163.2 (dt, $J$ = 25.4, 7.2 Hz). **HPLC conditions**: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (95:5), 0.8 mL/min, detector 210 nm, retention time, 16.4 (minor), 21.1 (major) min.

The more polar diastereoisomer: Rf (hexane/ethyl acetate 2:1) = 0.17 (Mostaine). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.33 (d, $J$ = 6.6 Hz, 3H, CH$_3$), 2.45-2.74 (m, 2H), 2.81 (br, 1H, OH), 4.18-4.33 (m, 1H), 4.38-4.52 (m, 2H); $^{13}$C NMR (50.3 MHz, CDCl$_3$): $\delta$ 16.4 (d, $J$ = 5.4 Hz), 30.2 (d, $J$ = 22.6 Hz), 65.7 (d, $J$ = 2.75 Hz), 69.0 (d, $J$ = 25.6 Hz), 95.7 (d, $J$ = 185.4 Hz), 172.5 (d, $J$ = 23.6 Hz, CO, ester); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -164.6 (dt, $J$ = 24.1, 13.9 Hz). **HPLC conditions**: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (95:5), 0.8 mL/min, detector 210 nm, retention time, 22.9 (minor), 25.7 (major) min.

**MS m/z** (relative intensity): 148.05 (M+, 1.38), 18, 43, 55, 91, 104 (100), 122, 131, 149; **Anal. Calcd** for $C_6H_9FO_3$: C, 48.65; H, 6.12. Found: C, 48.36; H, 6.31.

2-Fluoro-2-(1-hydroxyethyl)butyrolactone or 3-Fluoro-3-(1-hydroxyethyl)-2(3H)-furanone (P9)

**S,S-Ru**

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<td>S,S-Ru</td>
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<td>Substrate</td>
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<td>Isopropanol</td>
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<tr>
<td>Time</td>
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<tr>
<td>Purification (FC)</td>
<td>hexane:EtOAc 2:1</td>
<td></td>
</tr>
</tbody>
</table>

Product: an oil, 67 mg, 91% with dr = 1:1 ($^{19}$F NMR) (96%, 86% ee)

$C_6H_9FO_3$ (Mr = 148.132).

The less polar diastereoisomer: Rf (hexane/ethyl acetate 2:1) = 0.25 (Mostaine). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.37 (d, $J$ = 6.4 Hz, 3H, CH$_3$), 2.42 (d, $J$ = 5.6 Hz, 1H, OH), 2.30-2.54 (m, 1H), 2.60-2.90 (m, 1H), 4.27-4.41 (m, 1H), 4.36-4.51 (m, 2H); $^{13}$C NMR (62.9 MHz, CDCl$_3$): $\delta$ 16.8, 28.2 (d, $J$ = 21.8 Hz), 65.9 (d, $J$ = 1.9 Hz), 66.5 (d, $J$ = 30.1 Hz), 95.4 (d, $J$ = 186.9 Hz), 173.4 (d, $J$ = 22.6 Hz, CO, ester); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -163.2 (dt, $J$ =
3. Experimental Part

25.4, 7.1 Hz). **HPLC conditions**: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (95:5), 0.8 mL/min, detector 210 nm, retention time, 17.2 (major), 20.8 (minor) min.

The more polar diastereoisomer: $R_f$ (hexane/ethyl acetate 2:1) = 0.17 (Mostaine). **$^1$H NMR** (200 MHz, CDCl$_3$): $\delta$ 1.32 (d, J = 6.4 Hz, 3H, CH$_3$), 2.39-2.78 (m, 2H), 2.86 (br, 1H, OH), 4.16-4.33 (m, 1H), 4.38-4.56 (m, 2H), **$^{13}$C NMR** (62.9 MHz, CDCl$_3$): $\delta$ 16.5 (d, J = 5.3 Hz), 30.2 (d, J = 22.6 Hz), 65.7 (d, J = 2.0 Hz), 69.0 (d, J = 25.6 Hz), 95.7 (d, J = 186.5 Hz), 172.5 (d, J = 23.6 Hz, CO, ester), **$^{19}$F NMR** (188.3 MHz, CDCl$_3$): $\delta$ -164.7 (dt, J = 23.9, 14.1 Hz). **HPLC conditions**: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (95:5), 0.8 mL/min, detector 210 nm, retention time, 23.3 (major), 24.7 (minor) min.

**MS m/z** (relative intensity): 148.10 (M$^+$, 0.35), 18 (100), 43, 57, 71, 89, 104 (100), 123, 131, 149; **Anal. Calcd** for C$_6$H$_9$F$_3$O$_3$: C, 48.65; H, 6.12. Found: C, 48.63; H, 6.18.

**3-Fluoro-3-(1-hydroxyethyl)-1-phenyl-2-pyrrolidinone (P10)**

**$R,R$-Ru**

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<th>Component</th>
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Purification (FC) hexane:TBME 1:1

Product 74.5 mg, 96% with dr = 6:1 ($^{19}$F NMR) (98%, 96% ee)

**C$_{12}$H$_{14}$FNO$_2$** (Mr = 223.24). $R_f$ (hexane/TBME 1.2)0.34 (Mostaine).

**$^1$H NMR** (300 MHz, CDCl$_3$): $\delta$ 1.26 (d, J = 5.1 Hz, 3H, CH$_3$, minor), 1.32 (dd, J = 6.3, 1 Hz, 3H, CH$_3$, major), 2.21-2.33 (m, 1H), 2.51-2.69 (m, 1H), 2.78 (br, 1H, OH), 3.77-3.81 (m, 1H), 3.88-4.00 (m, 1H), 7.20 (t, J = 7.2 Hz, 1H, Ar), 7.38 (t, J = 8.0 Hz, 2H, Ar), 7.63 (d, J = 7.5 Hz, 2H, Ar); **$^{13}$C NMR** (75 MHz, CDCl$_3$): $\delta$ 16 (CH$_3$), 25.8 (d, J = 22 Hz, CH$_2$, major), 26 (d, J = 23 Hz, CH$_2$, minor), 45 (s, CH$_2$N$_2$) 67 (d, J = 31 Hz, CH, major), 70 (d, J = 25 Hz, CH, minor), 99 (d, J = 184 Hz, CF), 120 (C), 126 (C), 129 (C), 130 (C), 169 (d, J = 22 Hz, CO), **$^{19}$F NMR** (188.3 MHz, CDCl$_3$): $\delta$ -159.9 to -158.3 (m, major), -163 to -164 (m, minor); **HRMS (EI)**: Calcd for C$_{12}$H$_{14}$FNO$_2$ 223.1009, Found 223.1011. **HPLC conditions**: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (95:5), 1.0 mL/min, detector 210 nm, retention time, 20.1, 22.0 (major), 41.1 (major), and 43.2 min.

**3-Fluoro-3-(1-hydroxyethyl)-1-phenyl-2-pyrrolidinone (P10)**

**$S,S$-Ru**

<table>
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<th>Component</th>
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Purification (FC) hexane:TBME 1:1

Product 42 mg, 76% with dr = 2:1 ($^{19}$F NMR) (95%, 99% ee)

**C$_{12}$H$_{14}$FNO$_2$** (Mr = 223.24). $R_f$ (hexane/TBME 1.2)0.34 (Mostaine).

**$^1$H NMR** (300 MHz, CDCl$_3$): $\delta$ 1.26 (d, J = 5 Hz, 3H, CH$_3$, minor), 1.32 (dd, J = 6 Hz, 3H, CH$_3$, major), 2.21-2.33 (m, 1H), 2.51-2.69 (m, 1H), 2.78 (br, 1H, OH), 3.77-3.81 (m, 1H), 3.88-4.00 (m, 1H), 7.20 (t, J = 7.2 Hz, 1H, Ar), 7.38 (t, J = 8.0 Hz, 2H, Ar), 7.63 (d, J = 7.5 Hz, 2H, Ar); **$^{13}$C NMR** (75 MHz, CDCl$_3$): $\delta$ 16 (CH$_3$), 25.8 (d, J = 22 Hz, CH$_2$, major), 26 (d, J = 23 Hz, CH$_2$, minor), 45 (s, CH$_2$N$_2$) 67 (d, J = 31 Hz, CH, major), 70 (d, J = 25 Hz, CH, minor), 99 (d, J = 184 Hz, CF), 120 (C), 126 (C), 129 (C), 130 (C), 169 (d, J = 22 Hz, CO), **$^{19}$F NMR** (188.3 MHz, CDCl$_3$): $\delta$ -159.9 to -158.3 (m, major), -163 to -164 (m, minor); **HRMS (EI)**: Calcd for C$_{12}$H$_{14}$FNO$_2$ 223.1009, Found 223.1011. **HPLC conditions**: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (96:4), 1.0 mL/min, detector 210 nm, retention time, 20.1, 22.0 (major), 41.1 (major), and 43.2 min.
3. Experimental Part

(1H), 2.51-2.69 (m, 1H), 2.86 (br, OH), 3.77-3.81 (m, 1H), 3.88-4.00 (m, 1H), 4.32-4.38 (m, 1H), 7.20 (t, J = 7.2 Hz, 1H, Ar), 7.38 (t, J = 8.0 Hz, 2H, Ar), 7.63 (d, J = 7.5 Hz, Ar); \(^{13}\text{C} \text{NMR} \) (75 MHz, CDCl\textsubscript{3}): \( \delta \) 16 (CH\textsubscript{3}), 25.8 (d, J = 22 Hz, CH\textsubscript{2}, major), 26 (d, J = 23 Hz, CH\textsubscript{2}, minor), 45 (s, CH\textsubscript{2}N), 67 (d, J = 31 Hz, CH, major), 70 (d, J = 25 Hz, CH, minor), 99 (d, J = 184 Hz, CF), 120 (C), 126 (C), 129 (C), 139 (C), 169 (CO); \(^{19}\text{F} \text{NMR} \) (188.3 MHz, CDCl\textsubscript{3}): \( \delta \) -159.9 to -158.3 (m, major), -163 to -164 (m, minor); HRMS (EI): Calcd for C\textsubscript{12}H\textsubscript{14}FN\textsubscript{2}O\textsubscript{2} 223.1009, Found 223.1011. HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (96:4), 1.0 mL/min, detector 210 nm, retention time, 20.0 (major), 22.2, 41.0, and 43.2 (major) min.

Ethyl 2-chloro-3-hydroxy-2-methyl-3-phenylpropionate (P11)

\( R,R-Ru \) 1.4 mg, 0.0025 mmol, 1mol%

<table>
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<th>Substance</th>
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<th>Time</th>
<th>Purification (FC)</th>
<th>Product</th>
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</table>

\( \text{C}_{12}\text{H}_{15}\text{ClO}_{3} \) (M\(_{r}\) = 242.70). \( R_f \) (hexane/TBME 3:1) = 0.30 (KMnO\textsubscript{4}). \(^{1}\text{H} \text{NMR} \) (250 MHz, CDCl\textsubscript{3}): \( \delta \) 1.28 (t, J = 7.5 Hz, 3H, CH\textsubscript{2}CH\textsubscript{3}), 1.30 (t, J = 7.2 Hz, 3H, CH\textsubscript{2}CH\textsubscript{3}), 1.60 (s, 1.7H, CH\textsubscript{3}), 1.66 (s, 1.3H, CH\textsubscript{3}), 3.07 (s, OH), 3.08 (s, OH), 4.25 (q, J = 6.8 Hz, 2H, CH\textsubscript{2}CH\textsubscript{3}), 5.22 (s, CHO\textsubscript{H}), 5.23 (s, CHO\textsubscript{H}), 7.31-7.46 (m, 5H, Ph). HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:1), 0.6 mL/min, detector 210 nm, retention time, 51.1, 58.6 (major), 65.9 (major), 83.1 min.

Ethyl 2-chloro-3-hydroxy-2-methyl-3-phenylpropionate (P11)

\( S,S-Ru \) 1.4 mg, 0.0025 mmol, 1mol%

<table>
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<th>Substance</th>
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<th>Time</th>
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<th>Product</th>
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\( \text{C}_{12}\text{H}_{15}\text{ClO}_{3} \) (M\(_{r}\) = 242.70). \( R_f \) (hexane/TBME 3:1) = 0.30 (KMnO\textsubscript{4}). \(^{1}\text{H} \text{NMR} \) (250 MHz, CDCl\textsubscript{3}): \( \delta \) 1.28 (t, J = 7.5 Hz, 3H, CH\textsubscript{2}CH\textsubscript{3}), 1.30 (t, J = 7.2 Hz, 3H, CH\textsubscript{2}CH\textsubscript{3}), 1.60 (s, 1.7H, CH\textsubscript{3}), 1.66 (s, 1.3H, CH\textsubscript{3}), 3.07 (s, OH), 4.25 (q, J = 6.8 Hz, 2H, CH\textsubscript{2}CH\textsubscript{3}), 5.22 (s, CHO\textsubscript{H}), 7.31-7.46 (m, 5H, Ph). HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:1), 0.6 mL/min, detector 210 nm, retention time, 51.0 (major), 59.4, 67.8, 84.4 (major) min.

Benzyl 2-chloro-3-hydroxy-2-methylbutanoate (P12)

\( R,R-Ru \) 1.6 mg, 0.0027 mmol, 1mol%

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3. Experimental Part

Time 72 h
Purification (FC) hexane:TBME 3:1
Product oil, 49.6 mg, 77% with dr = 1:1 (92%, 87% ee)
(Note: 9.1 mg of the starting material benzyl 2-methyl-3-oxobutanoate was recovered as a racemic mixture)

C_{12}H_{15}ClO_3 (M_r = 242.699). R_f (hexane/TBME 3:1) = 0.69 (KMN0_4).
The less polar diastereoisomer: \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\ 1.21\ (d, J = 6.3\ Hz, \text{CH}_3), 1.70\ (s, \text{CH}_3), 2.53\ (d, J = 6.0\ Hz, \text{OH}), 4.17-4.29\ (m, 1H), 5.23\ (s, \text{CH}_2), 7.30-7.41\ (m, \text{5H, Ar}); \(^{13}\text{C NMR}\) (75.5 MHz, CDCl\(_3\)): \(\delta\ 17.5\ (\text{CH}_3), 23.1\ (\text{CH}_3), 68.0\ (\text{CH}_2), 74.1\ (\text{C}), 72.3\ (\text{CH}), 128.2, 128.6, 128.8, 135.2\ (\text{C}), 170.7\ (\text{COO, ester}).

The more polar diastereoisomer: \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\ 1.26\ (d, J = 6.3\ Hz, \text{CH}_3), 1.75\ (s, \text{CH}_3), 2.49\ (d, J = 6.0\ Hz, \text{OH}), 4.17-4.29\ (m, 1H), 5.23\ (s, \text{CH}_2), 7.30-7.41\ (m, \text{5H, Ar}); \(^{13}\text{C NMR}\) (75.5 MHz, CDCl\(_3\)): \(\delta\ 17.4\ (\text{CH}_3), 22.2\ (\text{CH}_3), 67.9\ (\text{CH}_2), 71.4\ (\text{C}), 72.0\ (\text{CH}), 128.1, 128.6, 128.8, 135.2\ (\text{C}), 170.8\ (\text{COO, ester}).

HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (99:1), 0.5 mL/min, detector 210 nm, retention time, 55.4 (major), 67.7 (major), 90.7, 97.8 min.

Benzyl 2-chloro-3-hydroxy-2-methylbutanoate (P12)

\(S,S-Ru\) 1.5 mg, 0.0025 mmol, 1mol% 
Substrate 60 mg, 0.25 mmol 
Isopropanol 4 mL 
Time 72 h 
Purification (FC) hexane:TBME 3:1 
Product oil, 28 mg, 46% with dr = 1:1 (93%, 87% ee)
(Note: 22 mg of the starting material benzyl 2-methyl-3-oxobutanoate was recovered as a racemic mixture)

C_{12}H_{15}ClO_3 (M_r = 242.699). R_f (hexane/TBME 3:1) = 0.69 (KMN0_4).
The less polar diastereoisomer: \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\ 1.22\ (d, J = 6.3\ Hz, \text{CH}_3), 1.70\ (s, \text{CH}_3), 2.53\ (br, \text{OH}), 4.18-4.29\ (m, 1H), 5.23\ (s, \text{CH}_2), 7.33-7.36\ (m, \text{5H, Ar}); \(^{13}\text{C NMR}\) (75.5 MHz, CDCl\(_3\)): \(\delta\ 17.4\ (\text{CH}_3), 23.0\ (\text{CH}_3), 67.9\ (\text{CH}_2), 74.0\ (\text{C}), 71.2\ (\text{CH}), 128.1, 128.5, 128.7, 135.1\ (\text{C}), 170.6\ (\text{CO}).

The more polar diastereoisomer: \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\ 1.27\ (d, J = 6.3\ Hz, \text{CH}_3), 1.76\ (s, \text{CH}_3), 2.43\ (d, J = 6.0\ Hz, \text{OH}), 4.18-4.29\ (m, 1H), 5.23\ (s, \text{CH}_2), 7.33-7.36\ (m, \text{5H, Ar}); \(^{13}\text{C NMR}\) (75.5 MHz, CDCl\(_3\)): \(\delta\ 17.4\ (\text{CH}_3), 22.2\ (\text{CH}_3), 67.9\ (\text{CH}_2), 71.3\ (\text{C}), 71.9\ (\text{CH}), 128.0, 128.5, 128.7, 135.1\ (\text{C}), 170.8\ (\text{CO}).

HPLC conditions: Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (99:1), 0.5 mL/min, detector 210 nm, retention time, 65.1, 77.4, 90.7 (major), 97.8 (major) min.

Diphenylmethyl 2-chloro-3-hydroxy-2-methylpentanoate (P13)

\(R,R-Ru\) 1.7 mg, 0.0028 mmol, 1 mol%
3. Experimental Part

Substrate 92.7 mg, 0.28 mmol,  
\([\alpha]_D = -5.08 (c = 1.23, \text{MeOH})\)

Isopropanol 2.5 mL

Time 72 h

Purification (FC) hexane:TBME 3:1

Product oil (9.7 mg, 10%) with dr = 74:26 (93%, 58% ee),  
(Note: 80 mg of the starting material was recovered)

C\(_{19}\)H\(_{21}\)ClO\(_3\) (Mr = 332.82). R\(_r\) (hexane/TBME 3:1) = 0.34 (UV, KMnO\(_4\)). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta 0.99 (t, J = 7.0 \text{ Hz}, 3H, CH\(_3\)CH\(_2\)), 1.26-1.41 (m, 1H, CH\(_2\)CH\(_3\)), 1.56-1.66 (m, 1H, CH\(_2\)CH\(_3\)), 1.71 (s, CH\(_3\), major), 1.78 (s, CH\(_3\), minor), 2.16 (d, \(J = 7.0 \text{ Hz}, 0.2H, \text{OH}, \text{minor})\), 2.33 (d, \(J = 5.8 \text{ Hz}, 0.8H, \text{OH}, \text{major})\), 3.94 (q, \(J = 5.8 \text{ Hz}, 1H, \text{CH})\), 6.90 (s, 1H, CHPh\(_2\)), 7.24-7.36 (m, 10H, 2Ar).  

HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:1), 1.0 mL/min, detector 210 nm, retention time, 12.6, 13.5 (major), 15.5, 16.8 (major) min.

Diphenylmethyl 2-chloro-3-hydroxyl-2-methylpentanoate (P13)

\(\text{S,S-Ru}\)  
Substrate 105.7 mg, 0.32 mmol,  
\([\alpha]_D = -5.08 (c = 1.23, \text{MeOH})\).

Isopropanol 2.5 mL

Time 72 h

Purification (FC) hexane:TBME 3:1

Product oil, 8.4 mg, 8% with dr = 12:88 (52%, 93% ee)  
(Note: the starting material recovered 93.4 mg)

C\(_{19}\)H\(_{21}\)ClO\(_3\) (Mr = 332.82). R\(_r\) (hexane/TBME 3:1) = 0.34 (UV, KMnO\(_4\)). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \(\delta 0.99 (t, J = 7.4 \text{ Hz}, 3H, CH\(_2\)CH\(_2\)), 1.26-1.47 (m, 1H, CH\(_2\)CH\(_3\)), 1.56-1.70 (m, 1H, CH\(_2\)CH\(_3\)), 1.71 (s, 0.6H, CH\(_3\), minor), 1.78 (s, 2.4H, CH\(_3\), major), 2.17 (d, \(J = 7.3 \text{ Hz}, 0.8H, \text{OH}, \text{major})\), 2.33 (d, \(J = 5.8 \text{ Hz}, 0.2H, \text{OH}, \text{minor})\), 3.89-3.97 (m, 1H, CH), 6.90 (s, 1H, CHPh\(_2\)), 7.30-7.36 (m, 10H, 2Ar).  

HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:1), 1.0 mL/min, detector 210 nm, retention time, 12.4, 13.5 (major), 14.7 (major), 17.0 min.

Ethyl 2-chloro-2-fluoro-3-hydroxy-3-phenylpropionate (P14)

\(\text{R,R-Ru}\)  
Substrate 60 mg, 0.25 mmol

Isopropanol 2 mL

Time 20 h

Purification (FC) hexane:TBME 3:1

Product oil, 29 mg, 48% with dr = 27:73 (92%, 36% ee)

C\(_{11}\)H\(_{12}\)ClFO\(_3\) (Mr = 246.663).  
The less polar diastereoisomer: R\(_r\) (hexane/TBME 3:1) = 0.38 (Mostaine). \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta 1.24 (t, J = 7.2 \text{ Hz}, 3H, \text{CH})\), 3.00 (br, OH), 4.24 (q, \(J = 7.2, 2H, \text{CH}_2\)), 5.23 (d, \(J = 7.8 \text{ Hz}, 1H, \text{CO})\), 7.22 (d, \(J = 7.8 \text{ Hz}, 1H, \text{CHPh})\), 7.30-7.36 (m, 10H, 2Ar).
3. Experimental Part

15.6, 1H, CH), 7.36-7.49 (Ar, m, 5H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 13.4 (CH$_3$), 63.6 (CH$_2$O), 76.9 (d, $J = 21.4$ Hz, CH), 106.0 (d, $J = 264.3$ Hz, CF), 128.3 (d, $J = 1.8$ Hz, CH), 128.5 (CH), 129.4 (CH), 134.9 (C), 165.4 (d, $J = 26.8$ Hz, CO); $^{19}$F NMR (188.13 MHz, CDCl$_3$): $\delta$ -129.58 (d, $J = 15.6$ Hz). **HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:2:0.8), 0.5 mL/min, detector 210 nm, retention time, 83.3 and 103.2 min.

The more polar diastereoisomer: $R_f$ (Hexane/TBME 3:1) = 0.31 (Mostaine). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.37 (t, $J = 7.2$ Hz, 3H, CH$_3$), 3.19 (br, OH), 4.38 (q, $J = 7.2$, 2H, CH$_2$), 5.19 (d, $J = 20.2$ Hz, 1H, CH), 7.36-7.49 (Ar, m, 5H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.0 (CH$_3$), 63.7 (CH$_2$O), 77.7 (d, $J = 21.3$ Hz, CH), 104.2 (d, $J = 264.8$ Hz, CF), 128.4 (CH), 128.6 (d, $J = 1.7$ Hz, CH), 129.4 (CH), 135.2 (C), 165.5 (d, $J = 28.8$ Hz, CO); $^{19}$F NMR (188.13 MHz, CDCl$_3$): $\delta$ -135.477 (d, $J = 20.1$ Hz). **HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:2:0.8), 0.5 mL/min, detector 210 nm, retention time, 110.2 and 124.0 min.

**Ethyl 2-chloro-2-fluoro-3-hydroxy-3-phenylpropionate (P14)**

| $S,S$-Ru | 1.5 mg, 0.0025 mmol, 1 mol% |
| Substrate | 57 mg, 0.25 mmol |
| Isopropanol | 2 mL |
| Time | 20 h |
| Purification (FC) | hexane:TBME 3:1 |
| Product | oil, 4.8 mg, 8.2%, $dr = 11.89$ (78%, 73% ee) |

(Note: substrate mostly recovered)

C$_{11}$H$_{12}$ClF$_3$O$_3$ (M$_r$ = 246.663).

The less polar diastereoisomer, $R_f$ (hexane/TBME 3:1) = 0.38 (Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.24 (t, $J = 7.2$ Hz, 3H, CH$_3$), 3.21 (s, OH), 4.25 (q, $J = 7.2$, 2H, CH$_2$), 5.23 (d, $J = 15.6$, 1H, CH), 7.37-7.50 (Ar, m, 5H); $^{19}$F NMR (188.13 MHz, CDCl$_3$) $\delta$ -129.57 (d, $J = 15.6$ Hz). **HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:2:0.8), 0.5 mL/min, detector 210 nm, retention time, 82.8 and 104.3 min.

The more polar diastereoisomer: $R_f$ (hexane/TBME 3:1) = 0.31 (Mostaine). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.37 (t, $J = 7.2$ Hz, 3H, CH$_3$), 3.21 (s, OH), 4.39 (q, $J = 7.2$, 2H, CH$_2$), 5.22 (d, $J = 20.2$ Hz, 1H, CH), 7.37-7.50 (Ar, m, 5H); $^{19}$F NMR (188.13 MHz, CDCl$_3$): $\delta$ -135.4 (d, $J = 20$ Hz). **HPLC conditions:** Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (99:2:0.8), 0.5 mL/min, detector 210 nm, retention time, 110.5 and 120.7 min.

**Determination of the Absolute Configuration of an $\alpha$-Fluoro-$\beta$-hydroxy Amide and $\alpha$-Fluoro-$\beta$-hydroxy Ester via the Derivatization and X-Ray Crystallography**

3-Fluoro-3-(1-hydroxyethyl)-1-phenyl-2-pyrrolidinone (P10, $dr = 1:2.1$, 90%, 96% ee)
3. Experimental Part

3-Acetyl-3-fluoro-1-phenyl-2-pyrrolidinone (100 mg, 0.45 mmol, 53% ee, prepared by asymmetric fluorination under catalysis of S,S-Ti) and transfer hydrogenation with S,S-Ru (2.5 mg, 0.0045 mmol, 1 mol%) in 3 mL of propanol were stirred under argon at room temperature for 10 h. The reaction mixture was concentrated under vacuo. The residue was purified by flash chromatography on silica gel using 1:1 hexane-TBME mixture as eluent to afford the products (44 mg, 43.6%) and recover the substrate (43 mg).

The less polar diastereoisomer (14 mg, 90% ee): C_{12}H_{14}FN_{2}O_{2} (M_r = 223.24). R_f (hexane/TBME 1:2) = 0.34 (UV, KMnO_4). ^1H NMR (200 MHz, CDCl_3): δ 1.31 (d, J = 6.4 Hz, 3H, CH_3), 2.13-2.31 (m, 1H), 2.47-2.74 (m, 2H), 3.75-4.00 (m, 2H), 4.31(dq, J = 10 Hz, 7Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 8.2 Hz, 2H), 7.65 (d, J = 8.0 Hz). ^19F NMR (188.3 MHz, CDCl_3): δ -158.1 (dt, J = 26 Hz, 6.5 Hz). HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (96:4), 1.0 mL/min, detector 210 nm, retention time, 20.5 (major) and 23.0 min.

The more polar diastereoisomer (30 mg, 96% ee): C_{12}H_{14}FN_{2}O_{2} (M_r = 223.24). R_f (hexane/TBME 1:2) = 0.40 (UV, KMnO_4). ^1H NMR (200 MHz, CDCl_3): δ 1.25 (d, J = 6.4 Hz, 3H, CH_3), 2.12-2.52 (m, 2H), 3.69-3.81 (m, 2H), 3.87-3.99 (m, 2H), 4.22(dq, J = 16 Hz, 7 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.63 (d, J = 8.2 Hz). ^19F NMR (188.3 MHz, CDCl_3): δ -164.0 to -164.3 (m). HPLC conditions: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (96:4), 1.0 mL/min, detector 210 nm, retention time, 20.5, 22.8, 41.9, 43.2 (major) min.

Bicyclo[2.2.1]heptane-1-methanesulfonic acid-7, 7-dimethyl-2-oxo-, 1-(3-fluoro-1-phenyl-2-oxo-pyrrolidin-3-yl)ethyl ester (17, racemic mixture)

At 0 °C, to a solution of 3-fluoro-3-(1-hydroxyethyl)-1-phenyl-2-pyrodinone (P10, racemic mixture of the more polar diastereoisomer) (80 mg, 0.36 mmol) and DMAP (40 mg, 0.36 mmol) in 4 mL of dichloromethane (1S)-(+)-camphor-10-sulfonyl chloride (90 mg, 0.36 mmol) was added. Stirring was continued for 2h at 0°C, and then 24 hours at room temperature before water (10 mL) was added. The reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic phase was washed with brine, dried over MgSO_4, concentrated in vacuo. The product was purified by flash chromatography on silica gel (hexane:ethyl acetate = 2:1) to afford (74.9 mg, 48%) as a white solid, and the substrate was recovered (40 mg).

C_{22}H_{28}FNO_{5}S (M_r = 437.52). R_f (hexane/ethyl acetate 2:1) = 0.24 (UV, Mostaine). ^1H NMR (200 MHz, CDCl_3): δ 0.87 (s, CH_3-camphor, 3H), 0.88 (s, CH_3-camphor, 3H), 1.10 (s, CH_3-camphor, 3H), 1.13-1.47 (m, 1H, CH_2-6'), 1.58-1.75 (m, CH_2-6', 1H), 1.51 (d, J = 6.6 Hz, CH_3-7, 3H), 1.92 (d, J = 18.4 Hz, CH_2-3', 2H), 2.01-2.16 (m, CH-4', 1H), 2.33-2.48 (m, CH_2-5', 2H), 2.48-2.80 (m, CH_2-4, 2H), 3.09 (d, J = 15.0 Hz, CH_2-10', 1H), 3.14 (d, J = 15.0 Hz, CH_2-10', 1H), 3.66 (d, J = 15.0 Hz, CH_3-10', 1H), 3.68 (d, J = 15.0 Hz, CH_3-10', 1H), 3.78-4.03 (m, CH_2-5, 2H), 5.19-5.34 (m, CH-6, 1H), 7.22 (t, J = 7.2 Hz, 1H, Ph), 7.41 (t, J = 7.6 Hz, 2H, Ph), 7.65 (d, J = 8.2 Hz, 2H, Ph); ^13C NMR (75.5 MHz, CDCl_3): δ 16.5 (d, J = 5.5
3. Experimental Part

Hz, CH$_3$-7), 16.0 (d, J = 6.0 Hz, CH$_3$-7), 19.7 (CH$_3$-camphor), 19.8 (CH$_3$-camphor), 25.0 (CH$_2$-5'), 25.2 (CH$_2$-5'), 25.86 (d, J = 23.6 Hz, CH$_3$-4), 25.9 (d, J = 23.1 Hz, CH$_3$-4), 26.9 (CH$_2$-6'), 42.5 (CH$_3$-3'), 42.8 (CH-4'), 44.8 (CH$_2$-5), 48.0 (C-7'), 48.4 (CH$_2$-10'), 48.5 (CH$_2$-10'), 58.0 (C-5'), 58.1 (C-5'), 79.0 (d, J = 27.0 Hz, CHO-6), 79.2 (d, J = 27.4 Hz, CHO-6), 97.5 (d, J = 187.3 Hz, C-3), 97.6 (d, J = 186.7 Hz, C-3), 120.2 (CH), 126.0 (CH), 129.2 (CH), 138.2 (C), 166.6 (d, J = 22.0 Hz, CON), 166.7 (d, J = 22.1 Hz, CON), 213.9 (CO), 214.0 (CO); $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -149.8 (td, J = 22.9, 10.3 Hz), -150.3 (td, J = 22.8, 10.3 Hz).

Bicyclo[2.2.1]heptane-1-methanesulfonic acid-7,7-dimethyl-2-oxo-, l-(3-fluoro-l-phenyl-2-oxo-pyrrolidin-3-yl)ethyl ester (17)

A solution of starting material (P10, the less polar diastereoisomer, 98% ee, 10 mg, 0.045 mmol), DMAP (cat) and 0.5 mL of Et$_3$N in 2 mL of dichloromethane was cooled to 0 °C and S-camphorsulfonyl chloride (44.8 mg, 0.18 mmol, 4 eq) was added. Stirring was continued for 2 h at 0 °C, and then 3 d at room temperature before the addition of water (10 mL) was added. The reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL). The organic phase was washed with dilute HCl and brine, dried over MgSO$_4$, concentrated in vacuo. The product was purified by flash chromatography on silica gel (hexane:ethyl acetate = 2:1) to afford 8 mg (41%) as a thick oil.

C$_{22}$H$_{28}$FNO$_5$S (Mr = 437.52). R$_f$ (hexane/ethyl acetate 2:1) = 0.34 (UV, Mostaine). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.81 (s, CH$_3$-camphor, 3H), 0.99 (s, 3H, CH$_3$-camphor), 1.02-2.82 (m, 12H), 2.88 (d, J = 14.8 Hz, 1H, CHHSO$_2$), 3.73 (d, J = 14.8 Hz, 1H, CHHSO$_2$), 3.80-4.00 (m, CH$_2$N, 2H), 5.13-5.27 (m, 1H, CHOSO$_2$), 7.21 (t, J = 7.4 Hz, 1H, Ph), 7.40 (t, J = 7.4 Hz, 2H, Ph), 7.85 (d, J = 8.0 Hz, 2H, Ph), $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -160.38 (td, J = 25.0, 8.8 Hz).

Bicyclo[2.2.1]heptane-1-methanesulfonic acid-7, 7-dimethyl-2-oxo-, (1R)-1-((1S)-3-fluoro-1-phenyl-2-pyrrolidinyl)ethyl ester (1S*,4R*) (17)

A solution of 3-fluoro-3-(1-hydroxyethyl)-1-phenyl-2-pyrrolidinone (P10, the more polar diastereoisomer, 30 mg, 96% ee) and DMAP (22.6 mg, 0.2 mmol, 1.5 eq) in 2 mL of dichloromethane was cooled to 0 °C and S-camphorsulfonyl chloride (40 mg, 0.16 mmol, 1.2 eq.) was added. Stirring was continued for 2 h at 0 °C, and then 3 d at room temperature before water (10 mL) was added. The reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL). The organic phase was washed with brine, dried over MgSO$_4$, concentrated in vacuo. The product was purified by flash chromatography on silica gel (hexane:ethyl acetate = 2:1) to afford product 17 (9.5 mg, 9%) as a white solid, and substrate was recovered (20 mg). Single crystals for X-ray crystallography were grown in pentane-CD$_2$Cl$_2$ solution.

C$_{22}$H$_{28}$FNO$_5$S (Mr = 437.52). R$_f$ (hexane/ethyl acetate 1:2) = 0.24 (UV, Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.98 (s, CH$_3$-camphor, 3H), 1.21 (s, CH$_3$-camphor, 3H), 1.37-1.46 (s,
3. Experimental Part

(1S)-(−)-Camphanic acid-1-(tetrahydro-3-fluoro-2-oxo-3-furanyl)ethyl ester (18)

(1S)-(−)-Camphanic acid chloride (44 mg, 0.202 mmol, 2.0 equiv) was added to a mixture of 3-fluoro-3-(1-hydroxyethyl)-2(3H)-furanone (15 mg, 0.101 mmol, 87% ee, the more polar diastereoisomer P9 obtained by asymmetric transfer hydrogenation of racemic S9 with R,R-Ru) and DMAP (24.7 mg, 0.202 mmol, 2 eq) in 5 mL of dry dichloromethane. The mixture was stirred for 10 h at room temperature and it was then poured into dilute HCl (2 M) and extracted twice with dichloromethane. The combined organic layers were washed successively with HCl (2 M), saturated NaHCO₃ and water, then dried (MgSO₄) and concentrated. The crude product was purified by column chromatography on SiO₂ with hexane/ethyl acetate 1:1, to give product 18 as a white solid (29 mg, 87%). The crystals for X-ray crystallography were grown in a solution of dichloromethane overlaid with pentane. C₁₆H₁₁FO₆ (Mr = 328.333). Rₚ (hexane/ethyl acetate 1:1) = 0.18 (weak with Mostaine). ¹H NMR (250 MHz, CDCl₃): δ 0.99 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 1.14 (s, 3H, CH₃), 1.42 (d, J = 6.5 Hz, 3H, CH₃), 1.66-1.76 (m, CH₂, 1H), 1.90-2.14 (m, CH₂, 2H), 2.42-2.77 (m, CH₂, 3H), 4.36-4.55 (m, 2H, CH₂O), 5.57 (dq, J = 13.0, 6.5 Hz, 1H, CH); ¹³C NMR (62.9 MHz, CDCl₃): δ 9.7 (CH₃), 14.6 (d, J = 5.8 Hz, CH₃), 16.5 (CH₃), 16.7 (CH₃), 28.8 (CH₂), 30.3 (d, J = 22.8 Hz, CH₂), 30.6 (CH₂), 54.4 (C), 54.8 (C), 65.1 (d, J = 2.5 Hz, CH₂O), 70.9 (d, J = 25.9 Hz, CHO), 90.9 (C), 93.9 (d, J = 189.4 Hz, CF), 166.4 (CO), 170.2 (d, J = 23.0 Hz, CO), 178.0 (CO); ¹⁹F NMR (188.3 MHz, CDCl₃): δ -161.2 (td, J = 23.9, 14.1 Hz); MS m/z (relative intensity): 328 (M⁺, 3.79), 96, 140, 189, 217, 235 (100.00), 279, 351 (MNa⁺); HRMS (MALDI): Calcd for [C₁₆H₁₁FO₆ + Na] 351.1214, Found 351.1210; Anal. Calcd for C₁₆H₁₁FO₆: C, 58.53; H, 6.45. Found: C, 59.08; H, 6.72.

(R)-(+)−1,1′-Binaphthyl-2,2′-diyl Phosphorochloridate BNP−Cl (19)

Phosphorus oxychloride (535.5 mg, 325.5 μL, 3.49 mmol) in 10 mL of benzene was added slowly to a mixture of (R)-(+)−1,1′-bi-2-naphthol (1.0 g, 3.49 mmol) and triethylamine (4 eq) in 20 mL of benzene at room temperature.
3. Experimental Part

temperature, resulted in the formation of a precipitate. After stirring at room temperature for 15 h the reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuo. Purification of the residue by column chromatography gave the compound as white solid (507.8 mg, 40%).

**C<sub>20</sub>H<sub>12</sub>ClO<sub>3</sub>P** (Mr = 366.734). \(^1\)H NMR (300 MHz, CDCl<sub>3</sub>): \(\delta\) 7.31-7.45 (m, 4H), 7.51-7.57 (m, 3H), 7.63 (d, \(J = 8.7\) Hz, 1H), 7.99 (dd, \(J = 7.8, 5.1\) Hz, 2H), 8.09 (dd, \(J = 9.0, 5.1\) Hz, 2H); \(^13\)C NMR (75.5 MHz, CDCl<sub>3</sub>): \(\delta\) 120 (d, \(J = 3.8\) Hz), 120.4 (d, \(J = 2.8\) Hz), 126.5, 127.2, 127.3, 127.4, 128.7, 131.8, 132.0, 132.1; \(^{31}\)P NMR (121 MHz, CDCl<sub>3</sub>): \(\delta\) 11.0 (s).

**Pentanoic acid-3-[(4-oxidodinaphtho[2,1d:1’,2’-f][1,3,2]dioxaphosphepin-4-yl)oxy]-phenyl ester, stereoisomer (9CI)**

Or **Pentanoic acid-3-(dinaphtho[2,1d:1’,2’-f][1,3,2]dioxaphosphepin-4-yloxy)-phenyl ester, Poxide, stereoisomer (20)**

1,1’-Binaphthyl-2,2’-diyl phosphorochloridate 19 (286 mg, 0.78 mmol, 1.9 eq) was added to a solution of phenyl 2-fluoro-2-methyl-3-hydroxy propanoate (90 mg, 0.4 mmol, dr = 5:1 (98%, 38% ee) in 2 mL of dichloromethane containing 1 mL of 1-methylimidazol. After the mixture was stirred for 24 h at room temperature, the solvent was evaporated under HV. The residue was purified by flash chromatography (hexane:ethyl acetate 10:1 to 3:1) to give a white powder as product (208 mg, 94%).

**C<sub>32</sub>H<sub>26</sub>FO<sub>6</sub>P** (Mr = 566.517). \(^1\)H NMR (200 MHz, CDCl<sub>3</sub>): \(\delta\) 1.28 (m, 3H, CH<sub>3</sub>), 1.74-2.10 (m, 2H, CH<sub>2</sub>), 1.94 (d, \(J = 21.6\) Hz, 3H, CH<sub>3</sub>), 5.26 (ddd, \(J = 23.4, 9.6, 3.4\) Hz, 1H, CH), 7.06-7.09 (m, 2H, Ar), 7.23-7.53 (m, 9H, Ar), 7.68 (dd, \(J = 8.6, 1.5\) Hz, 2H, Ar), 7.86-7.91 (m, 2H, Ar), 7.99 (d, \(J = 8.4\) Hz, 1H, Ar), 8.10 (d, \(J = 8.8\) Hz, 1H, Ar); \(^{19}\)F NMR (188.3 MHz, CDCl<sub>3</sub>): \(\delta\) -158.9 (m); \(^{31}\)P NMR (81 MHz, CDCl<sub>3</sub>): \(\delta\) 3.6 (s); MS m/z (relative intensity): 557 (M<sup>+</sup>, 100), 96, 189, 209, 349, 463; HRMS (MALDI): Calcd for C<sub>20</sub>H<sub>12</sub>ClO<sub>3</sub>P 557.1524, Found 557.1515; Anal. Calcd for C<sub>32</sub>H<sub>26</sub>FO<sub>6</sub>P: C, 69.06; H, 4.71. Found: C, 68.81; H, 5.05.

**Phenyl 2-fluoro-3-hydroxy-2-methylpentanoate (P3, dr = 5:1, 98%, 38% ee)**

Phenyl 2-fluoro-2-methyl-3-oxo-pentanoate (160 mg, 0.7 mmol, 78% ee, prepared by asymmetric fluorination with catalyst \(RR\)-TiI) and \(SS\)-Ru (4.2 mg, 0.007 mmol, 1 mol%) in isopropanol (4 mL) were stirred under argon at room temperature 20 h. The reaction mixture was concentrated under vacuo. The residue was purified by flash chromatography on silica gel using hexane/TBME (5:1 to 3:1) mixture as eluent to afford the product as a white solid (153.4 mg, 38%) with dr = 5:1 (98%, 38% ee).

**C<sub>12</sub>H<sub>15</sub>FO<sub>3</sub>** (Mr = 226.24). Rt (hexane/TBME 3:1) = 0.3 (KMnO<sub>4</sub>). \(^1\)H NMR (200 MHz, CDCl<sub>3</sub>): \(\delta\) 1.10 (t, \(J = 7.2\) Hz, 3H, CH<sub>3</sub>/CH<sub>2</sub>, major), 1.70 (d, \(J = 21.6\) Hz, 3H, CH<sub>3</sub>, minor), 1.75 (d, \(J = 22.2\) Hz, 3H, CH<sub>3</sub>, major), 1.45-1.95 (m, 2H, CH<sub>2</sub>/CH<sub>3</sub>), 2.30 (br, OH ), 3.88-3.90 (m, 1H, CHO), 7.13-7.19 (m, 2H, Ph), 7.27 (t, \(J = 7.2\) Hz, 1H, Ph), 7.41 (t, \(J = 7.5\) Hz, 2H,
3. Experimental Part

Ph); \(^{19}\text{F NMR}\) (188.3 MHz, CDCl\(_3\)): \(\delta -165.3\) (qd, \(J = 22.0, 17.7\) Hz, major), -168.9 (pentet, \(J = 21.5\) Hz, minor). **HPLC conditions**: Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (98:2), 1.0 mL/min, detector 254nm, retention time: 17.2 (major); 20.6 (major), 22.0 (minor).

**Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, 1-ethyl-1-(1-fluoro-1-methyl-2-oxo-3-phenyl-ethanoate-3-yl)methyl ester (21)**

A solution of phenyl-2-fluoro-3-hydroxy-2-methylpentanoate (40 mg, 0.092 mmol, dr = 10:1, 98% and 33% ee) and DMAP (cat) in 2 mL of dichloromethane and 0.5 mL of triethylamine was cooled to 0 °C and \(\text{S-camphorsulfonyl chloride} (182.3\) mg, 0.707 mmol, 4.0 eq) was added. Stirring was continued for 2 h at 0 °C, and then the solution was warmed slowly to room temperature. The reaction mixture was stirred for 1 d at room temperature before water (10 mL) was added. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL). The organic phase was washed successively with dilute HCl, saturated NaHCO\(_3\), brine, and dried over MgSO\(_4\), and concentrated under vacuo. The product was purified by flash chromatography on silica gel (hexane:ethyl acetate = 2:1) to afford brownish oil as product (48.6 mg, 62.4%).

\(\text{C}_{22}\text{H}_{29}\text{FO}_{6}\) (M\(_r = 440.525\). \(R_f\) (hexane/TBME 2:1) = 0.31 (Mostaine). \(^{1}\text{H NMR}\) (200 MHz, CDCl\(_3\)): \(\delta 0.90\) (s, 3H, CH\(_3\)-camphor), 1.11 (s, 3H, CH\(_3\)-camphor), 1.83 (d, \(J = 22.0\) Hz, 3H, CH\(_3\)CF), 1.11-2.78 (m, 12H), 3.30 (d, \(J = 15.0\) Hz, 1H, CH\(_3\)SO\(_2\)), 3.78 (d, \(J = 15.0\) Hz, 1H, CH\(_3\)SO\(_2\)), 5.08 (ddd, \(J = 17.0, 9.6, 3.8\) Hz, 1H, CH\(_3\)SO\(_2\)), 7.16-7.20 (m, 2H, Ar), 7.42-7.49 (m, 2H, Ar), \(^{19}\text{F NMR}\) (188.3 MHz, CDCl\(_3\)): \(\delta -158.1\) (m).

\(\text{(1S)-(\text{-})-Camphanic acid-2-ethoxycarbonyl-2-fluoro-cyclohexyl ester (22)}\)

(1S)-(\text{-})-Camphanic acid chloride (68 mg, 0.316 mmol, 2.0 equiv) was added to a mixture of ethyl 1-fluoro-2-hydroxy-cyclohexane carboxylate (P\(_8\), 30 mg, 0.158 mmol, enantiomerically pure, the more polar diastereoisomer obtained by reduction of S\(_8\) with \(\text{S,S-Ru}\)) and DMAP (38 mg, 0.316 mmol, 2 eq) in 5 mL of dry dichloromethane. The mixture was stirred for 10 h at room temperature and it was then poured into dilute HCl (2 M) and extracted twice with dichloromethane. The combined organic layers were washed successively with HCl (2 M), saturated NaHCO\(_3\), and water, then dried (Na\(_2\)SO\(_4\)) and concentrated. The crude product was purified by column chromatography on SiO\(_2\) with hexane/ethyl acetate 2:1, to give the product as a white solid (23 mg, 39%).

\(\text{C}_{16}\text{H}_{21}\text{FO}_{6}\) (M\(_r = 370.413\). \(R_f\) (hexane/ethyl acetate 2:1) = 0.27 (weak Mostaine). \(^{1}\text{H NMR}\) (250 MHz, CDCl\(_3\)): \(\delta 0.95\) (s, 3H, CH\(_3\)), 1.06 (s, 3H, CH\(_3\)), 1.18 (s, 3H, CH\(_3\)), 1.30 (d, \(J = 7.25\) Hz, 3H, CH\(_3\)), 1.50-2.45 (m, CH\(_3\)), 4.22 (q, \(J = 7.25\) Hz, CH\(_2\)), 5.35 (ddd, \(J = 24, 12.75, 5.0\) Hz, 1H, CH\(_3\)), \(^{13}\text{C NMR}\) (62.9 MHz, CDCl\(_3\)): \(\delta 9.6\) (CH\(_3\)), 14.0 (CH\(_2\)), 16.4 (CH\(_3\)), 16.6 (CH\(_3\)), 23.1 (d, \(J = 1.6\) Hz, CH\(_2\)), 28.9 (CH\(_2\)), 30.6 (CH\(_2\)), 32.9 (d, \(J = 22.1\) Hz, CH\(_2\)), 53.9 (C), 54.7 (C), 62.0 (CH\(_2\)O), 74.2 (d, \(J = 18.8\) Hz, CHO), 91.0 (C), 93.7 (d, \(J = \)...
3. Experimental Part

194.5 Hz, CO), 166.0 (d, J = 26.9 Hz, CO), 177.8 (CO), the CH$_3$, CH$_2$ or CH was determined by 13C-DEPT-135° and proton and carbon was assigned by CH-HMQC; $^{19}$F NMR (188.3 MHz, CDCl$_3$): $\delta$ -181.5 (b).

3.2 Experimental Part of Chapter 2 - Asymmetric 1,4-Addition of 1,3-Dicarbonyl Compounds to Alkenenitriles

Preparation of Ni(Pigiphos) Complexes

In all synthesis of Ni complexes, generally carried out on a small scale the yield was not determined, but is expected to be close to quantitative.

[Ni(Pigiphos)(CH$_3$CN)](BF$_4$)$_2$ (Ni$_A$)

(R)-S-Pigiphos (908.6 mg, 1 mmol) and [Ni(H$_2$O)$_6$][(BF$_4$)$_2$] (69.2 mg, 0.2 mmol) was suspended in 10 mL of acetonitrile at room temperature. The solution was stirred for 6 h and the solvent was removed under reduced pressure to afford the black solid. The resulting solid was washed with hexane 3 times and dried under HV.

C$_{56}$H$_{58}$B$_2$F$_8$Fe$_2$NiP$_3$ (Mr = 1181.9814). $^1$H NMR (300 MHz, CD$_3$CN): $\delta$ 0.48-2.06 (m, 17H, Cy and 2CH$_3$CH), 3.38 (m, 1H, CHCH$_3$), 3.71 (m, 1H, CHCH$_3$), 3.88 (s, 5H, Cp), 4.16 (s, 5H, Cp'), 4.70 (m, 2H), 4.75 (m, 1H), 4.83 (m, 1H), 4.95 (s, 1H), 5.05 (s, 1H), 6.90-7.96 (m, 20H, Ar); $^{31}$P NMR (121.5 MHz, CD$_3$CN): $\delta$ 8.62-11.74 (m, PAr$_2$), 17.2-20.7 (m, PAr$_2$), 74.4-85.3 (m, PCy); Anal. Calcd for C$_{56}$H$_{58}$B$_2$F$_8$Fe$_2$NiP$_3$: C, 56.91; H, 4.95, N, 1.19. Found: C, 56.60; H, 5.11, N, 1.53.

[Ni(Pigiphos)(methacrylonitrile)](BF$_4$)$_2$ (Ni$_B$)

(R)-S-Pigiphos (908.625 mg, 1 mmol) and [Ni(H$_2$O)$_6$][2BF$_4$] (340.4 mg, 1 mmol) were suspended in 10 mL of methacrylonitrile at room temperature. The solution was stirred for 6 h and the solvent was removed under reduced pressure to afford the black solid. The resulting solid was washed with hexane 3 times and dried under HV.

C$_{58}$H$_{68}$B$_2$F$_8$Fe$_2$NiP$_3$ (Mr = 1208.0176). $^1$H NMR (300 MHz, CD$_2$Cl$_2$): $\delta$ 0.6-2.63 (m, 11H, Cy, 6H, 2CH$_3$CH and 3H, CH$_3$CMeCN), 3.47 (m, 1H), 3.70 (m, 1H), 3.88 (s, 5H, Cp), 4.16 (s, 5H, Cp'), 4.65 (m, 1H), 4.78 (m, 2H), 4.99 (m, 1H), 5.04 (m, 1H), 5.35 (m, 1H), 5.73 (s, 2H, CH$_2$CCH$_3$CN), 6.94-7.98 (m, 20H, 4Ph); $^{31}$P NMR (121.5 MHz, CD$_2$Cl$_2$): $\delta$ 11.8 (m, PA$r_2$), 18.7 (m, PA$r_2$), 84 (m, PCy); Anal. Calcd for C$_{58}$H$_{68}$B$_2$F$_8$Fe$_2$NiP$_3$CH$_2$Cl$_2$ (Mr = 1292.951): C, 54.58; H, 4.83; N, 1.08 Found: C, 54.17; H, 5.13; N, 1.08.
3 Experimental Part

\[
\text{[Ni(Pigiphos)(THF)](BF}_4\text{)}_2
\]

(R)-(S)-Pigiphos (908.625 mg, 1 mmol) and \([\text{Ni(H}_2\text{O)}_6\text{]}(\text{BF}_4\text{)}_2\) (340.4 mg, 1 mmol) were suspended in 10 mL of methacrylonitrile at room temperature. The solution was stirred for 6 h and the orange precipitate was formed. The solvent was removed (cannula) and the solid was washed with hexane, dried under HV.

\[
\text{C}_{58}\text{H}_{63}\text{B}_2\text{F}_4\text{Fe}_2\text{NNiP}_3 \ (M_r = 1213.035). \ \text{\textsuperscript{1}H NMR (300 MHz, CD}_2\text{C}_2\text{Cl}_2): } \delta 0.6-1.92 \ (m, \ 11 \text{H, Cy and } 6 \text{H, } 2\text{CH}_3\text{CH}), 2.44 \ (br, \ 1 \text{H, CH}_3\text{CH}), 2.65 \ (br, \ 1 \text{H, CH}_3\text{CH}), 2.89 \ (br, \ 1 \text{H, THF}), 3.30 \ (br, \ 1 \text{H, THF}), 3.46 \ (br, \ 1 \text{H, THF}), 3.71 \ (s, \ 5 \text{H, Cp}), 3.93 \ (s, \ 5 \text{H, Cp}), 4.26 \ (s, \ 1 \text{H}), 4.56 \ (s, \ 1 \text{H}), 4.61 \ (s, \ 1 \text{H}), 4.68 \ (s, \ 1 \text{H}), 4.87 \ (s, \ 1 \text{H}), 4.94 \ (s, \ 1 \text{H}), 7.27-7.88 \ (m, \ 20 \text{H, } 2\text{Ph}), 31\text{P NMR (121.5 MHz, CD}_2\text{C}_2\text{Cl}_2): } \delta 7.76 \ (dd, J = 73.3, 53.3 \text{ Hz, PAr}_2), 9.12 \ (t, J = 59.7 \text{ Hz, PAr}_2), 72.4 \ (q, J = 74.7 \text{ Hz, PCy}); \text{ Anal. Calcd for } \text{C}_{58}\text{H}_{60}\text{OB}_2\text{F}_8\text{Fe}_2\text{NNiP}_3\text{C}_6\text{H}_{14} \ (M_r = 1299.211): \text{ C, 59.17; H, 5.97. Found: C, 59.09; H, 5.51.}

\[
\text{[Ni(Pigiphos-3,5-CF}_3\text{-Ar})(\text{CH}_3\text{CN})](\text{BF}_4\text{)}_2 \ (\text{NiF})
\]

(R)-(S)-Pigiphos-3,5-CF\text{3Ar} (240 mg, 0.20 mmol) and \([\text{Ni(H}_2\text{O)}_6\text{]}(\text{BF}_4\text{)}_2\) (69.2 mg, 0.2 mmol) were suspended in 10 mL of acetonitrile at room temperature. The solution was stirred for 6 h and the solvent was removed under reduced pressure to afford the brown solid. The resulting solid was washed with hexane 3 times and dried under HV.

\[
\text{C}_{60}\text{H}_{74}\text{B}_2\text{F}_2\text{Fe}_2\text{NNiP}_3 \ (M_r = 1453.9722). \ \text{\textsuperscript{1}H NMR (300 MHz, CD}_2\text{C}_2\text{Cl}_2): } \delta 0.48-2.06 \ (m, \ 17 \text{H, Cy and } 2\text{CH}_3\text{CH}), 2.37 \ (m, 1 \text{H}), 2.80 \ (m, \ 1 \text{H}), 3.90 \ (s, \ 5 \text{H, Cp}), 4.18 \ (s, \ 5 \text{H, Cp}), 4.66 \ (s, \ 1 \text{H}), 4.77 \ (m, \ 2 \text{H}), 4.98 \ (1 \text{H}, 5.02 \ (s, \ 1 \text{H}), 5.33 \ (s, \ 1 \text{H}), 6.88-7.92 \ (m, \ 12 \text{H, Ar}), 31\text{P NMR (121.5 MHz, CD}_2\text{C}_2\text{Cl}_2): } \delta 8.49-10.8 \ (m, \ \text{PAr}_2), 17.0-19.0 \ (m, \ \text{PAr}_2), 83.2-84.5 \ (m, \ \text{PCy}).
\]

\[
\text{[Ni(Pigiphos-3,5-CH}_3\text{-Ar})(\text{acetonitrile})](\text{BF}_4\text{)}_2 \ (\text{NiF})
\]

(R)-(S)-Pigiphos-3,5-CH\text{3Ar} (510 mg, 0.5 mmol) and \([\text{Ni(H}_2\text{O)}_6\text{]}(\text{BF}_4\text{)}_2\) (170 mg, 0.5 mmol) were suspended in 20 mL of acetonitrile at room temperature. The solution was stirred for 12 h and the solvent was removed under reduced pressure to afford the black solid. The resulting solid was washed with hexane 3 times and dried under HV (547 mg, 84.5 %).

\[
\text{C}_{64}\text{H}_{74}\text{B}_2\text{F}_2\text{Fe}_2\text{NNiP}_3 \ (M_r = 1294.193). \ \text{\textsuperscript{1}H NMR (250 MHz, CD}_2\text{C}_2\text{Cl}_2): } \delta 0.59-2.25 \ (m, \ 44 \text{H, Cy, 8CH}_3\text{-Ar, CH}_3\text{CH and CH}_3\text{CN}), 3.13 \ (br, \ 1 \text{H, CHCH}_3), 3.86 \ (br, \ 1 \text{H,}
\]
3. Experimental Part

$\text{CHCH}_3$, 3.97 (s, 5H, Cp), 4.18 (s, 5H, Cp'), 4.30, 4.64, 4.77, 4.80, 5.02 and 5.11 (s, 1H, C$_2$H$_5$), 6.45 (br, d, 2H, Ar), 7.06 (s, 1H, Ar), 7.11 (s, 2H, Ar), 7.41 (s, 3H, Ar), 7.63 (br, d, 2H, Ar), 7.78 (br, d, 2H, Ar), $^{31}$P NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ 8.84 (dd, $J = 200, 75$ Hz, PAr$_2$), 20.3 (dd, $J = 203.1, 66.2$ Hz, PAr$_2$), 86.5 (br t, $J = 73$ Hz, PCy); $^{19}$F NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ -151.5 and -149 (br, BF$_4$); Anal. Calcd for C$_{64}$H$_{74}$B$_2$F$_8$Fe$_2$NiP$_3$: C, 59.40; H, 5.76; N, 1.08. Found: C, 58.55; H, 5.66; N, 1.02.

$[\text{Ni}(\text{Pigiphos})(P25)](\text{BF}_4)_2$

A solution of 3-(2-cyanopropyl)-3-methyl-2,4-pentanedione (P25) in 0.5 mL of ether was added to a solution of $[\text{Ni}(\text{Pigiphos})(\text{THF})](\text{BF}_4)_2$ in 1 mL of dichloromethane. The mixture was stirred 12 h and concentrated. The residue was washed with pentane three times and dried under HV.

C$_{64}$H$_{70}$B$_2$F$_8$Fe$_2$NiO$_2$P$_3$ (Mr = 1322.1600). $^1$H NMR (250 MHz, CD$_2$Cl$_2$): $\delta$ 0.63-2.16 (m), 3.63, 3.75, 3.86, 4.13, 4.72, 5.36 (all signals are broad because the complex is paramagnetic); $^{31}$P NMR (1012 MHz, CD$_2$Cl$_2$): $\delta$ 6.97-7.05 (m, PAr$_2$), 7.74-8.65 (m, PAr$_2$), 69.1-72.42 (m, PCy). MS $m/z$ (relative intensity): 985, 965, 883, 845, 701, 621, 565, 485, 409; Anal. Calcd for C$_{64}$H$_{70}$B$_2$F$_8$Fe$_2$NiO$_2$P$_3$: C, 58.14; H, 5.34; N, 1.06 Found: C, 58.09; H, 5.42; N, 0.97.

Preparation of Racemic products of 1,4-Addition Reactions

$2$-tert-Butoxy carbonyl-2-(2-chloro-2-cyanoethyl)cyclopentanone (P43)

At room temperature DABCO (11.2 mg, 20 mol%) was added to a solution of tert-butyloxycarbonyl 2-oxo-cyclopentanecarboxylate (92 mg, 0.5 mmol) in 2 mL of solvent (toluene:2-chloroacrylonitrile 1:1). The reaction mixture was stirred for 50 h at room temperature. The reaction mixture was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (5:1) mixture as eluent to afford the product as colorless oil (103 mg, 76%).

C$_{13}$H$_{18}$ClNO$_3$ (Mr = 271.740). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.44 (s, 10H, 3CH$_3$), 1.98-2.13 (m, 3H), 2.21-2.37 (m, 2H), 2.43-2.75 (m, 3H), 4.92 (d, $J = 6.75, 5.7$ Hz, the less polar diastereomer), 4.96 (d, $J = 8.25, 4.5$ Hz, the more polar diastereomer); $^{13}$C NMR (75.5 MHz, CDCl$_3$): the less polar diastereomer: $\delta$ 19.72, 27.80, 34.0, 37.1, 38.9, 40.6, 59.14, 83.7, 117.4, 169.1, 213.0; the more polar diastereomer: $\delta$ 19.68, 27.79, 34.1, 37.2, 39.4, 39.9, 59.05, 83.5, 117.2, 169.0, 213.3; MS $m/z$ (relative intensity): 271.09 (M$^+$, 0.28), 41, 57 (100), 79, 113, 141, 198, 215, 256; HRMS (EI) Calcd for C$_{13}$H$_{18}$ClNO$_3$: C, 57.46; H, 6.68; N, 5.15. Found: C, 57.57; H, 6.72; N, 5.30.
Asymmetric Catalysis of 1,4-Addition of 1,3-Dicarbonyl Compounds to Vinlylnitrides

The Standard Procedure:
The reaction was performed using 0.25-0.5 mmol of 1,3-dicarbonyl compounds, 5 mol% of [Ni(Pigiphos)(NCMe)](BF$_4$)$_2$ Ni$_A$ or prepared in situ by treating 5 mol% of [Ni(H$_2$O)$_6$](BF$_4$)$_2$ with 5 mol% of Pigiphos, 5 mol% of base, in 2 mL of methacrylonitrile or acrylonitrile at 50 °C. Purification was achieved by flash chromatography affording the desired adduct.

Ethyl 2-(2-cyanopropyl)-3-oxo-3-phenylpropanoate (P23)
According to the standard procedure starting from 48 mg (0.25 mmol) of the β-keto ester gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (5:1) mixture as eluent to afford the product as colorless solid (54.4 mg, 84%) with dr = 1:1 (24%, 34% ee).

C$_{15}$H$_{17}$N$_3$O$_3$ (M$^+$ = 259.300). R$_f$ (hexane:ethyl acetate 4:1) = 0.30. $^1$H NMR (300 MHz, CDCl$_3$): δ 1.14 (t, J = 7.2 Hz, CH$_3$CH$_2$O), 1.18 (t, J = 7.2 Hz, CH$_3$CH$_2$O), 1.36 (d, J = 7.2 Hz, CH$_3$CHCN), 1.37 (d, J = 8.1 Hz, CH$_3$CHCN), 2.01-2.02 (m, CH$_2$), 2.27-2.47 (m, CH$_2$), 2.62-2.69 (m, CHCN), 2.82-2.89 (m, CHCN), 4.12 (q, J = 7.2 Hz, OCH$_2$CH$_3$), 4.17 (q, J = 7.2 Hz, OCH$_2$CH$_3$), 7.44-7.52 (m, 2H, Ar), 7.61 (d, J = 7.2 Hz, 1H, Ar), 8.00-8.03 (m, 2H, Ar), $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 14.0, 14.0, 18.4, 18.4, 23.9, 24.1, 32.9, 33.2, 51.6, 51.8, 62.0, 122.0, 122.2, 128.9, 128.9, 129.0, 129.0, 131.4, 131.4, 131.4, 136.1, 168.7, 1169.0, 194.0, 194.0; MS m/z (relative intensity): 259.12 (M$^+$, 0.47), 51, 77, 105 (100), 120, 133, 159, 192, 205, 214; HRMS (EI) Calcd for C$_{15}$H$_{17}$O$_3$ 259.1203 Found 259.1205; Anal. Calcd for C$_{15}$H$_{17}$O$_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.42; H, 6.63; N, 5.45. Diastereoselectivity determined by $^1$H NMR, dr = 1:1. Enantioselectivity determined by HPLC Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OJ, hexane:PrOH (96:4), 0.6 mL/min, detector 210 nm, retention time, 34.6 (major), 37.0 (minor), 40.5 (major) and 53.2 (minor) min.

Benzyl 2-acetyl-4-cyanopentanoate (P24a)
According to the standard procedure starting from 48 mg (0.25 mmol) of the β-keto ester gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (4:1) mixture as eluent to afford the product as colorless oil (16.2 mg, 25%) and double times addition product (benzyl 2-acetyl-2-(2-cyanoethyl)-4-cyanopentanoate) as white solid (30 mg, 37%).

C$_{15}$H$_{17}$N$_3$O$_3$ (M$^+$ = 259.300). $^1$H NMR (300 MHz, CDCl$_3$): δ 1.96-2.06 (m, 1H), 2.25 (d, J = 6.9 Hz, 3H, CH$_3$C), 2.24-2.77 (m, 1H, CH$_2$), 3.75-3.82 (m, 1H, CH), 5.18 (d, J = 18.3 Hz, 1H, CHH), 5.24 (d, J = 18.3 Hz, 1H, CHH), 7.32-7.40 (m, 5H, Ar); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 18.3, 18.4, 23.7, 23.9, 29.5, 30.1, 31.8, 32.0, 56.9, 57.3, 67.8, 67.9, 112.9, 122.1, 128.2, 128.5, 128.6, 128.8, 129.9, 135.0, 168.3, 168.5, 201.0, 201.4; MS
3. Experimental Part

Benzy 2-acetyl-2-(2-cyanoethyl)-4-cyanopentanoate (P24b)

C_{19}H_{22}N_{2}O_{3} (M_r = 326.390). *H NMR (300 MHz, CDCl$_3$): $\delta$ 1.26 (d, $J = 6.9$ Hz, 3H, CH$_3$), 1.35 (d, $J = 6.9$ Hz, 3H, CH$_3$), 2.05-2.52 (m, 6H), 2.17 (s, 3H, CH$_3$), 5.22 (d, $J = 12.2$ Hz, 1H, CHPh), 5.25 (d, $J = 12.2$ Hz, 1H, CHPh), 7.38 (s, 5H, Ar); MS m/z (relative intensity): 326, 16 (M+, 0.12), 43, 91 (100), 138, 145, 192, 230, 272, 298; HRMS (EI) Calcd for C$_{19}$H$_{22}$N$_{2}$O$_{3}$ 326.1625 Found 326.1624.

3-(2-Cyanopropyl)-3-methyl-2,4-pentanedione (P25)

According to the standard procedure starting from 72 mg (0.5 mmol) of the diketone gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (2:1) mixture as eluent to afford the product as oil (69.2 mg, 77%) with 44% ee.

C$_{10}$H$_{15}$NO$_{2}$ (M, = 181.232). R$_f$ (hexane/ethyl acetate 2:1) = 0.27 (Mostaine). *H NMR (300 MHz, CDCl$_3$): $\delta$ 1.25 (d, $J = 7.2$ Hz, 3H, CH$_3CH$), 1.48 (m, 3H, CH$_3C$), 2.13 (s, 3H, CH$_3CO$), 2.14 (s, 3H, CH$_3CO$), 2.01-2.18 (m, 2H, CH$_2$), 2.48-2.57 (m, 1H, CH); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 18.3 (CH$_3C$), 19.9 (CH$_3CH$), 21.5 (CH), 26.6 and 26.7 (2CH$_3CO$), 38.2 (CH$_2$), 65.5 (C), 122.7 (CN), 205.9 and 206.5 (2CO); MS m/z (relative intensity): 181.1 (M+, 0.1), 43 (100), 57, 85, 139, 182.1 (M+1) -; HRMS (EI) Calcd for C$_{10}$H$_{15}$NO$_{2}$ [M-C$_2$H$_2$O]: 139.0992. Found: 139.0992; Anal. Calcd for C$_{10}$H$_{15}$O$_{2}$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.03; H, 8.37; N, 7.80; IR (film, cm$^{-1}$): 2985.9 (w), 2240.1 (w), 1698.6 (s), 1460.8 (m), 1360.7 (s), 1000.0 (s). Enantioselectivity determined by HPLC Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OJ, hexane:PrOH (95:5), 0.8 mL/min, detector 210 nm, retention time, 44.5 (minor), 48.8 (major) min.

3-(2-Cyanopropyl)-3-ethyl-2,4-pentanedione (P26)

According to the standard procedure starting from 61 mg (0.5 mmol) of the diketone gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (3:1) mixture as eluent to afford the product as oil (84 mg, 90%) with 41% ee.

C$_{11}$H$_{17}$NO$_{2}$ (M$_r$ = 192.2582). R$_f$ (hexane/ethyl acetate 2:1) = 0.33 (Mostaine). *H NMR (300 MHz, CDCl$_3$): $\delta$ 0.86 (t, $J = 7.5$ Hz, 3H, CH$_3CH_2$), 1.24 (d, $J = 6.8$ Hz, 3H, CH$_3CH$), 1.64 (q, $J = 7.5$ Hz, 2H, CH$_2CH_3$), 1.82 (dd, $J = 14.1$, 5.7 Hz, 1H, CH/CHCN) 2.12 (dd, $J = 14.1$, 10.8 Hz, 1H, CH/CH/CHCN), 2.71-2.94 (m, 7H, 2 CH$_3$ and CHCN); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 8.2, 18.7 (CH$_3$CH), 21.7 (CHCN), 31.1 (CH$_3$), 35.4 and 35.8, 35.9, 60.3 (C), 121.8 (CN), 214.7 and 216.3 (2CO); MS m/z (relative intensity): 195.11 (M+, 0.08), 55, 83, 93, 111, 139 (100), 178; Anal. Calcd for C$_{11}$H$_{17}$NO$_{2}$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.93; H, 8.51; N, 7.19; IR (Film, cm$^{-1}$): 2238.5 (w), 1716.0 (s), 1458.9 (m), 1220.6 (m), 1085.8 (m). Enantioselectivity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6
3. Experimental Part

2-(2-Cyanopropyl)-2-methyl-1,3-cyclohexanedione (P27)

According to the standard procedure starting from 62 mg (0.5 mmol) of the diketone gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (2:1) mixture as eluent to afford the product as colorless oil (78.4 mg, 81%) with 54% ee.

C_{11}H_{15}NO_{2} (M_r = 193.242). R_f (hexane/ethyl acetate 1:1) = 0.49 (Mostaine). ^1H NMR (300 MHz, CDCl_3): δ 1.21 (d, J = 7.2 Hz, 3H, CH_3CH), 1.30 (s, 3H, CH_3), 1.88 (dd, J = 13.8, 6.0 Hz, 1H, CH/HCHCN), 2.00-2.11 (m, 2H, CH_2), 2.32 (dd, J = 13.7, 10.0 Hz, 1H, CH/HCHCN), 2.58-2.84 (m, 5H, 2 CH_2 and CHCN); ^13C NMR (75.5 MHz, CDCl_3): δ 17.5 (CH_2 in cyclohexanone), 19.0 (CH(CHCN)), 25.8 (CH_2CO), 37.0 (CH_2CHCN), 37.8 and 38.0 (2 CH_2CO in cyclohexanone), 63.5 (C), 122.5 (CN), 209.3 and 210.3 (2CO); MS m/z (relative intensity): 193.1 (M^+, 8.14), 111.1 (100), 139, 55, 69, 41, 43; HRMS (EI) Calcd for C_{11}H_{15}NO_{2} 193.1098 Found 193.1097; IR (film, cm^{-1}): 2981.0 (s), 2942.3 (s), 2238.3 (m), 1694.0 (s), 1455.5 (s), 1318.8 (s), 1132.1 (s), 1018.3 (s), 588.1 (w). Enantioselectivity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane:PrOH (98:2), 0.8 mL/min, detector 210 nm, retention time, 41.8 (minor), 46.4 (major) min.

2-(2-Cyanopropyl)-2-methyl-1,3-cyclopentanedione (P28)

According to the standard procedure starting from 56 mg (0.5 mmol) of the diketone gave the corresponding reaction mixture. It was was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (2:1) mixture as eluent to afford the product as colorless oil (88 mg, 99%) with 44% ee.

C_{10}H_{13}NO_{2} (M_r = 179.2157). R_f (hexane/ethyl acetate 1:1) = 0.46 (Mostaine). ^1H NMR (300 MHz, CDCl_3): δ 1.17 (s, 3H, CH_3), 1.24 (d, J = 6.9 Hz, 3H, CH_3CH), 1.81 (dd, J = 14.1, 5.7 Hz, 1H, CH/HCHCN) 2.14 (t, J = 12.6 Hz, 1H, CH/HCHCN), 2.70-2.95 (m, 5H, 2 CH_2 and CHCN); ^13C NMR (75.5 MHz, CDCl_3): δ 18.7 (CH(CHCN)), 21.6 (CHCN), 23.1 (CH_3), 34.9 and 35.0 (2 CH_2CO in cyclopentane), 55.8 (C), 121.8 (CN), 214.5 and 215.9 (2CO); MS m/z (relative intensity): 179.09 (M^+, 3.89), 41, 55, 79, 97, 125 (100), 139, 180; HRMS (EI) Calcd for C_{10}H_{13}NO_{2} 179.0941 Found 179.0940; Anal. Calcd for C_{10}H_{13}NO_{2}: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.73; H, 7.47; N, 7.84; IR (KBr, cm^{-1}): 2237.5 (w), 1721.9 (s), 1454.8 (m), 1417.3 (m), 1079.1 (m). Enantioselectivity determined by HPLC Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OJ, hexane:PrOH (95.5), 0.8 mL/min, detector 210 nm, retention time, 67.3 (major), 78.7 (minor) min.

2-(2-Cyanopropyl)-2-ethyl-1,3-cyclopentanedione (P29)

According to the standard procedure starting from 63 mg (0.5 mmol) of the
3. Experimental Part

diketone gave the corresponding reaction mixture. It was was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (4:1) mixture as eluent to afford the product as colorless oil (97 mg, 99%) with 41% ee.

**C_{11}H_{15}NO_2 (M_1 = 193.242).** \(^{1}H\) NMR (300.13 MHz, CDCl\(_3\)): \(\delta 0.84\) (t, \(J = 7.5\) Hz, 3H, \(CH_2CH_2\)), 1.23 (d, \(J = 7.25\) Hz, 3H, \(CH_3CH\)), 1.63 (q, \(J = 7.5\) Hz, 2H, \(CH_2CH_3\)), 1.81 (dd, \(J = 13.75, 5.75\) Hz, 1H, \(CHHCH\)), 2.10 (dd, \(J = 13.75, 10.75\) Hz, 1H, \(CHHCH\)), 2.69-2.89 (m, 5H, 4H of cyclopentane and 1H of CHCN); \(^{13}C\) NMR (75.5 MHz, CDCl\(_3\)): \(\delta 8.2\) (CH\(_3\)), 18.6 (CH\(_2\)), 21.5 (CH\(_3\)), 30.9 (CH\(_2\)), 35.3 (CH\(_2\)), 35.7 (CH\(_2\)), 35.8 (CH\(_2\)), 60.2 (C), 121.8 (CN), 214.6 (CO), 216.2 (CO); MS \(m/z\) (relative intensity): 193.11 (M\(^+\), 4.12), 55, 83, 111, 139 (100), 150, 169, 181; HRMS (El) Calcd for C\(_{11}\)H\(_{15}\)NO\(_2\) 193.1098 Found 193.1099; Anal. Calcd for C\(_{11}\)H\(_{15}\)NO\(_2\): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.16; H, 7.97; N, 7.32.

Enantioselectivity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane/IPrOH (99:1), 0.6 mL/min, detector 210 nm, retention time, 71.4 (minor), 75.4 (major) min.

**2-Phenyl-2-(2-cyanopropyl)-1,3-dihydro-1,3-dioxo-2H-indene (P30)**

According to the standard procedure starting from 111 mg (0.5 mmol) of the diketone gave the corresponding reaction mixture. It was was directly purified by flash chromatography on silica gel using hexane/ethyl acetate (4:1) mixture as eluent to afford the product as a white solid (131.6 mg, 92%) with 21% ee.

**C\(_{19}\)H\(_{15}\)NO\(_2\) (Mr = 289.3279).** R\(_f\) (hexane/ethyl acetate 2:1) = 0.47 (Mostaine). \(^{1}H\) NMR (250 MHz, CDCl\(_3\)): \(\delta 1.28\) (d, \(J = 7.0\) Hz, 3H, \(CH_2CH\)), 2.35 (dd, \(J = 14.0, 5.0\) Hz, 1H, \(CHHCHCN\)), 2.75 (dd, \(J = 14.0, 9.5\) Hz, 1H, \(CHHCHCN\)), 2.84-2.95 (m, 1H, CH), 7.27-7.38 (m, 3H, Ar), 7.44-7.49 (m, 2H, Ar), 7.86-7.93 (m, 2H, Ar), 8.02-8.11 (m, 2H, Ar); \(^{13}C\) NMR (62.9 MHz, CDCl\(_3\)): \(\delta 19.5\) (CH\(_3CH\)), 22.0 (CHCN), 39.1 (CH\(_2\)), 60.8 (C), 121.8 (CN), 123.9, 124.2, 126.9, 128.5, 129.3, 136.0, 136.3, 136.6, 141.4, 141.9, 199.5 and 200.3 (2CO, ketone); MS \(m/z\) (relative intensity): 289.11 (M\(^+\), 25.15), 77, 103, 117, 152, 178, 207, 235 (100); HRMS (El) Calcd for C\(_{19}\)H\(_{15}\)NO\(_2\) 289.1098 Found 289.1093; Anal. Calcd for C\(_{19}\)H\(_{15}\)NO\(_2\): C, 78.87; H, 5.23; N, 4.84. Found: C, 78.64; H, 5.28; N, 4.79; IR (KBr, cm\(^{-1}\)): 2200 (w), 1738.6 (s), 1703.0 (s), 1260.9 (s), 696.2 (w), 583.4 (w). Enantiomericity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) DP, hexane/PrOH (90:10), 0.8 mL/min, detector 210 nm, retention time, 27.6 (minor), 34.9 (major) min.

**2-tert-Butoxycarbonyl-2-(2-cyanoethyl)cyclopentanone (P31a)**

According to the standard procedure starting from 46 mg (0.25 mmol) of the diketone gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (5:1) mixture as eluent to afford the product as colorless oil (69.2 mg, 89%) with 14% ee.

**C\(_{10}\)H\(_{15}\)NO\(_2\) (M\(_1\) = 181.232).** R\(_f\) (hexane/ethyl acetate 4:1) = 0.30 (Mostaine). \(^{1}H\) NMR (250.13 MHz, CDCl\(_3\)): \(\delta 1.42\) (s, 9H, 3CH\(_3\)), 1.82-2.71 (m, 10H); \(^{13}C\) NMR (62.9 MHz,
3. Experimental Part

3.1 (CH2), 19.7 (CH2), 27.9 (CH3), 29.4, 34.2, 37.9, 59.2 (C), 83.0 (C), 119.7 (CN), 169.7 (COO, ester), 214.3 (CO, ketone); MS m/z (relative intensity): 237.14 (M+, 4.40), 41, 57 (100), 81, 108, 136, 153, 181, 209, 222; HRMS (EI) Calcd for C10H15NO2 237.1360 Found 237.1362; Anal. Calcd for C10H15NO2: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.78; H, 8.02; N, 6.00. IR (film, cm⁻¹): 2977.5 (w), 2248.0 (w), 1748.2 (s), 1445.1 (m), 1370.0 (s), 1149.5 (s), 845.0 (m). Enantioselectivity determined by HPLC Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OD-H, hexane:PrOH (98:2), 0.8 mL/min, detector 230 nm, retention time, 22.3 (minor), 25.2 (major) min.

2-tert-Butoxycarbonyl-2-(2,4-dicyanobutyl)cyclopentanone (P31b)

2-tert-Butoxycarbonyl-2-cyclopentanone (0.5 mmol, 92 mg) was added to a solution of [Ni(Pigiphos)(CH3CN)](BF4)2 (5 mol%) in 2 mL of methacrylonitrile. After the reaction mixture was stirred for 2 d at room temperature, the reaction mixture was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (4:1) mixture as eluent to afford 2-tert-butoxycarbonyl-2-(2-cyanoethyl)cyclopentanone (63.7 mg, 53.8%) and 2-tert-butoxycarbonyl-2-(2,4-dicyanobutyl)cyclopentanone (32.8 mg, 22.6%).

C10H12N2O3 (M = 230.3575). 1H NMR (300.13 MHz, CDCl3): δ 1.44 (s, 9H, 3CH3), 1.94-2.68 (m, 12H), 2.79-2.86 (m, 0.5 H, CHCN), 3.02-3.08 (m, 0.5 H, CHCN); 13C NMR (75.5 MHz, CDCl3): δ 15.2 (CH2), 19.7 and 19.9 (CH2), 27.1 (CH), 27.9 (CH3), 29.4 and 29.7 (CH2), 33.5 and 34.1 (CH2), 35.1 and 35.8 (CH2), 37.2 and 37.8 (CH2), 59.5 and 59.8 (C), 83.3 and 83.4 (C), 120.5 and 120.7 (CN), 169.4 and 169.7 (COO, ester), 213.9 and 214.1 (CO, ketone); MS m/z (relative intensity): 291.17 (MH+, 0.25), 57 (100), 97, 113, 189, 217, 234; HRMS (EI) Calcd for [MH-C4H9, C10H22N2O3H-C4H9] 2324.0999 Found 234.1000; Anal. Calcd for C16H22N2O3: C, 66.19; H, 7.64; N, 9.65. Found: C, 66.04; H, 7.68; N, 9.50. IR (film, cm⁻¹): 2977.7 (w), 2247.9 (w), 1748.1 (s), 1720.7 (s), 1455.3 (m), 1370.3 (m), 1150.0 (s), 844.2 (w), 737.4 (s).

Ethyl 2-acetyl-4-cyano-2-methyl butanoate (P32)

According to the standard procedure starting from 72 mg (0.5 mmol) of the β-keto ester gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (4:1) mixture as eluent to afford the product as colorless oil (65 mg, 66%) with 0% ee.

C10H12NO3 (M = 197.231). 1H NMR (300.13 MHz, CDCl3): δ 1.23 (t, J = 7.2 Hz, 3H, CH3CO), 1.34 (s, 3H, CH3), 1.97-2.08 (m, 1H, CHH), 2.11-2.45 (m, 1H, CHH), 2.12 (s, 3H, CH3CO), 2.32 (dt, J = 7.8, 2.4 Hz, 2H, CH2), 4.18 (q, J = 7.2 Hz, CH3CH2); 13C NMR (75.5 MHz, CDCl3): δ 12.9 (CH2), 13.9 (CH3), 19.1 (CH3CH2), 26.1 (CH3O), 30.5 (CH2), 58.4 (C), 61.9 (CH3O), 119.1 (CN), 171.5 (COO, ester), 204.1 (CO, ketone); Anal. Calcd for C10H12NO3: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.94; H, 7.67; N, 7.10. IR (film, cm⁻¹): 2986.3 (w), 2249.0 (w), 1713.6 (s), 1448.0 (m), 1260.0 (s), 1192.5 (s), 1102.7, 858.8 (m). Enantioselectivity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6
3. Experimental Part

mm) AD-H, hexane:PrOH (98:2), 0.8 mL/min, detector 210 nm, retention time, 36.2 (major), 40.2 (minor) min.

Ethyl-2-(2-cyanoethyl)-2-methyl-3-oxo-3-phenylpropanoate (P33)
According to the standard procedure starting from 52 mg (0.5 mmol) of the β-keto ester gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (5:1) mixture as eluent to afford the product as colorless oil (45 mg, 69%) with 18% ee.

C₁₅H₁₇N₃O₃ (Mᵣ = 259.300). ¹H NMR (300.13 MHz, CDCl₃): δ 1.06 (t, J = 7.2 Hz, 3H, CH₃CH₂), 1.56 (s, 3H, CH₃), 2.22-2.49 (m, 4H, CH₂CH₂CN), 4.15 (q, J = 7.2 Hz, 2H, CH₂O), 7.39-7.44 (m, 2H, Ar), 7.51-7.57 (m, 1H, Ar), 7.77-7.80 (m, 2H, Ar); ¹³C NMR (75.5 MHz, CDCl₃): δ 12.9 (CH₂), 13.8 (CH₃), 21.2 (CH₃), 32.6 (CH₂), 62.1 (CH₂O), 119.2 (CN), 128.6, 128.7, 133.2, 134.9, 172.9 (COO, ester), 196.3 (CO, ketone). Enantioselectivity determined by HPLC Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OJ, hexane:PrOH (90:10), 1.0 mL/min, detector 230 nm, retention time, 17.1 (minor), 18.7 (major) min.

2-Ethoxycarbonyl-2-(2-cyanoethyl)cyclohexanone (P34)
According to the standard procedure starting from 85 mg (0.5 mmol) of the β-keto ester gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (4:1) mixture as eluent to afford the product as colorless oil (80 mg, 72%) with 15% ee.

C₁₂H₁₇O₃ (Mᵣ = 223.268). ¹H NMR (300.13 MHz, CDCl₃): δ 1.26 (t, J = 7.2 Hz, 3H, CH₃CH₂), 1.43 (dt, J = 12.9, 3.9 Hz, 1H), 1.57-1.64 (m, 2H), 1.68-1.77 (m, 1H), 1.82-1.86 (m, 1H), 1.96-2.03 (m, 1H), 2.10-2.32 (m, 2H), 2.38-2.56 (m, 4H), 4.21 (q, J = 7.2 Hz); ¹³C NMR (75.5 MHz, CDCl₃): δ 13.0 (CH₂), 14.1 (CH₃), 22.5 (CH₂), 27.4 (CH₂), 30.8 (CH₂), 36.7 (CH₂), 40.9 (CH₂), 59.7 (C), 61.2 (CH₂O), 119.4 (CN), 171.0 (COO, ester), 207.2 (CO, ketone); MS m/z (relative intensity): 223 (M⁺), 101 (100), 29, 41, 53, 67, 81, 121, 155, 178; HRMS (EI): Calcd for C₁₂H₁₇O₃ 223.2303 Found 223.2303; Anal. Calcd for C₁₂H₁₇O₃: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.20; H, 7.68; N, 7.17. IR (film, cm⁻¹): 2942.8 (w), 2248.1 (w), 1712.8 (s), 1447.7 (m), 1196.2 (s), 1028.8 (w). Enantioselectivity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (95:5), 0.8 mL/min, detector 210 nm, retention time, 13.9 (major), 16.5 (minor) min.

2-tert-Butoxycarbonyl-2-(2-cyanoethyl)cyclohexanone (P35)
According to the standard procedure starting from 99 mg (0.5 mmol) of the β-keto ester gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (4:1) mixture as eluent to afford the product as colorless oil (115.8 mg, 92%) with 18% ee.
3. Experimental Part

C_{14}H_{21}N_{3}O_{3} (M_r = 251.3214). R_f (hexane/ethyl acetate 4:1) = 0.33 (Mostaine). \textsuperscript{1}H NMR (300.13 MHz, CDCl\textsubscript{3}): \( \delta \) 1.48 (s, 9H, 3CH\textsubscript{3}), 1.61-2.61 (m, 12H), 1.57-1.64 (m, 12H, 6CH\textsubscript{2}); \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): \( \delta \) 13.1 (CH\textsubscript{2}), 22.6 (CH\textsubscript{2}), 27.5 (CH\textsubscript{2}), 28.0 (CH\textsubscript{3}), 31.1 (CH\textsubscript{2}), 36.8 (CH\textsubscript{2}), 41.1 (CH\textsubscript{2}), 60.5 (C), 83.3 (C), 119.7 (CN), 170.3 (COO, ester), 207.5 (CO, keto); \textbf{Anal. Calcd} for C\textsubscript{14}H\textsubscript{21}N\textsubscript{3}O\textsubscript{3}: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.01; H, 8.30; N, 5.57. Enantioselectivity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (98:2), 0.6 mL/min, detector 230 nm, retention time, 19.6 (major), 21.3 (minor) min.

2-Acetyl-2-(2-cyanoethyl)butyrolactone (P36)

According to the standard procedure starting from 64 mg (0.5 mmol) of the \( \beta \)-keto ester gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (2:1) mixture as eluent to afford the product as colorless oil (85 mg, 94%) with 5% ee.

C_{9}H_{11}NO_{3} (M_r = 181.1885). \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}): \( \delta \) 2.11-2.42 (m, 5H), 2.23 (s, 3H, CH\textsubscript{3}), 2.84-2.92 (ddd, \( J \) = 13, 7, 3.5 Hz, 1H), 4.25 (q, \( J \) = 8.8 Hz, 1H), 4.39 (dt, \( J \) = 9, 3.5 Hz, 1H); \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): \( \delta \) 13.1, 25.9, 29.5, 29.9, 60.0, 66.0, 118.2 (CN), 174.5 (COO, ester), 201.1 (CO, keto); MS \( m/z \) (relative intensity): 259.12 (M\textsuperscript{+}, 0.47), 51, 77, 105 (100), 120, 133, 159, 192, 205, 214; \textbf{HRMS (EI) Calcd} for C\textsubscript{9}H\textsubscript{11}NO\textsubscript{3} \[ M+H \] \textsuperscript{+} 182.0812 Found 182.0810; \textbf{Anal. Calcd} for C\textsubscript{9}H\textsubscript{11}NO\textsubscript{3}: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.57; H, 6.11; N, 7.76. Enantioselectivity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AS, hexane:PrOH (80:20), 0.8 mL/min, detector 210 nm, retention time, 12.5 (major), 14.5 (minor) min.

3-Acetyl-3-(2-cyanoethyl)-1-phenyl-2-pyrrolidinone (P37)

According to the standard procedure starting from 50 mg (0.25 mmol) of the \( \beta \)-keto ester gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (2:1) mixture as eluent to afford the product as colorless solid (61.5 mg, 96%) with 12% ee.

C_{15}H_{16}N_{2}O_{2} (M_r = 256.300). R_f (hexane/ethyl acetate 1:1) = 0.38. \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}): \( \delta \) 1.97-2.09 (m, 1H), 2.34 (s, 3H, CH\textsubscript{3}), 2.37-2.49 (m, 6H), 2.79 (ddd, \( J \) = 13.0, 7.25, 3.5 Hz, 1H), 3.78-3.94 (m, 2H), 7.22 (t, \( J \) = 7.75 Hz, 1H, Ar), 7.42 (t, \( J \) = 7.5 Hz, 2H, Ar), 7.61 (d, \( J \) = 8.0 Hz, 2H, Ar); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}): \( \delta \) 13.2, 26.3, 26.4, 30.0, 46.1, 62.9, 119.0 (CN), 120.2, 125.7, 129.2, 138.8, 170.6 (CON), 203.8 (CO, keto); MS \( m/z \) (relative intensity): 256.12 (M\textsuperscript{+}, 13.93), 43, 77, 104, 174 (100), 203, 214; \textbf{HRMS (EI) Calcd} for C\textsubscript{15}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2} 256.1207 Found 256.1205; \textbf{Anal. Calcd} for C\textsubscript{15}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2}: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.12; H, 6.35; N, 10.87. Enantioselectivity determined by HPLC Agilent 1050, Daicel Chiracel Column (250 x 4.6 mm) AD-H, hexane:PrOH (80:20), 0.8 mL/min, detector 210 nm, retention time, 13.1 (major), 15.4 (minor) min.

2-Methyl-3-(phenylthio)propanenitrile (P39)
3. Experimental Part

According to the standard procedure but starting from 55 mg (0.5 mmol) of the \( \beta \)-keto ester and 1.1 eq of DBU at room temperature gave the corresponding reaction mixture. It was directly purified by flash chromatography on silica gel using hexane-ethyl acetate (20:1) mixture as eluent to afford the product as colorless oil (87.4 mg, 98%) with 0% ee.

\[ \text{C}_{10}\text{H}_{11}\text{NS} \quad (M_r = 177.2660) \]

\[ \text{R} \quad (\text{hexane/ethyl acetate 4:1}) = 0.43 \quad \text{(UV, Mostaine)} \]

\[ ^1\text{H} \text{ NMR (300.13 MHz, CDCl}_3): \delta 1.41 (d, J = 7.2 \text{ Hz, 3H, CH}_3), 2.75 \quad \text{(hextet, J = 7.2 Hz, 1H), 2.99 (dd, J = 13.8, 7.2 Hz, 1H), 3.18 (dd, J = 13.8, 7.2 Hz, 1H), 7.31-7.36 (m, 3H, Ph), 7.41-7.44 (m, 2H, Ph)} \]

\[ ^{13}\text{C} \text{ NMR (75.5 MHz, CDCl}_3): \delta 17.4 \quad \text{(CH}_3), 26.2 \quad \text{(CH), 38.4 \quad (CH}_2), 121.6 \quad \text{(CN), 127.7, 129.4, 131.3, 134.0 \quad (C)} \]

\[ \text{Anal. Calcd for C}_{10}\text{H}_{11}\text{NS: C, 67.76; H, 6.25; N, 7.90. Found: C, 67.79; H, 6.31; N, 7.84. Enantioselectivity determined by HPLC Agilent 1100, Daicel Chiracel Column (250 x 4.6 mm) OJ, hexane:PrOH (98:2), 0.6 mL/min, detector 254 nm, retention time, 40.2, 44.0 min.} \]

3.3 Preparation of Starting Materials

\((4R,5R)-2,2\text{-Dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester (44)}^6\)

To a solution of dimethyl-D-tartrate (17 g, 95 mmol) in 150 mL of acetone was added BF\(_3\) OEt\(_2\) (8.5 g, 60 mmol) dropwise at room temperature. After the solution turned red, 300 mL of saturated NaHCO\(_3\) was added and extracted with EtOAc (2 x 200 mL). The organic phase was washed with water and dried over MgSO\(_4\). Distillation of the crude product gave a yellow oily product (11.3 g, 54.4%).

\[ \text{C}_{9}\text{H}_{14}\text{O}_6 \quad (M_r = 218.20) \]

\[ ^1\text{H} \text{ NMR (300 MHz, CDCl}_3): \delta 1.49 (s, 6H, CH}_3), 3.82 (s, 6H, CH}_3), 4.81 (s, 2H, CH) \]

\((4R,5R)-2,2\text{-Dimethyl-\alpha,\alpha,\alpha,\alpha^\prime}\text{-tetra-1-naphthalenyl-1,3-dioxolane-4,5-dimethanol, (R,R)-TADDOLato (45)}^1\)

A solution of 1-bromonaphthalene (9.8 mL, 71.25 mmol) was added at room temperature to a suspension of Mg (1.732 g, 71.25 mmol) in dry THF (30 mL), such to keep the solvent refluxing. 15 min later a solution of \((4R,5R)-2,2\text{-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester (3.59 g, 16 mmol, 0.25 eq)}\) in 45 mL of THF was added dropwise over 20 min. The mixture was heated to reflux for 1.5 h and left overnight at room temperature to give a deep brown solution. Saturated NaHCO\(_3\) solution was added carefully to this solution until the mixture was brought to pH 8. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine, dried over MgSO\(_4\) and concentrated under vacuo to give a yellowish solid, which was recrystallized from pentane-toluene to yield the yellowish product (8.0 g, 74%).
3. Experimental Part

**Dichlorodiisoproxytitanium (or Dichlorobis(2-propanolato)-titanium) (47)**

To a solution of Ti(O^Pr)_4 (6.0 mL, 20 mmol) in 20 mL dry hexane, TiCl_4 (2.2 mL, 20 mmol) was added dropwise via syringe under Argon. The deep brown solution was stirred for 22 h at room temperature. The solvent was removed with cannula and the solid was washed three times with pentane. The white solid was dried under HV to give the product.

**Di-μ-chloro-bis[chloro(η^6-1-isopropyl-4-methyl-benzene)ruthenium(II)] [RuCl_2 (η^6-p-cymene)]_2 (48)**

A solution of hydrated ruthenium trichloride (approximating RuCl_3 3H_2O, containing 38-39% Ru) (4 g, 15.4 mmol) in 100 mL of ethanol was treated with 20 mL of α-phellandrene and heated under reflux for 4 h under Argon. The solution was allowed to cool to room temperature, and the red-brown microcrystalline product was filtered off (3.84 g). An additional amount (360 mg) was obtained by evaporating the mother liquid under reduced pressure to approximately half-volume and refrigerating overnight. The overall yield is 4.2 g (90%).

**Methylketene dimer (50)**

To a solution of triethylamine hydrochloride (100 mg) in 200 mL of ether, propinyl chloride (19.3 g, 200 mmol) was added rapidly through the condenser. To the agitated mixture was added triethylamine (21.1 g, 210 mmol) dropwise from the funnel at a rate to maintain refluxing. The mixture was stirred for 1 h and was allowed to stand for 2 d at room temperature. The mixture was filtered and the filtrate was evaporated and the residue was distilled to give a colorless oil (5.9 g, 53%).
3. Experimental Part

$^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 1.35 (d, $J = 7.5$ Hz, 3H), 1.62 (d, $J = 7.0$ Hz, 3H), 3.97 (q, $J = 7.5$ Hz, 1H), 4.74 (qd, $J = 7.0, 1.2$ Hz, 1H).

2,4,6-Triisopropylbenzyl alcohol (51)$^{11}$

A solution of 2,4,6-triisopropylbenzoyl chloride (4 g, 15 mmol) in 40 mL of Et$_2$O was added to a slurry of LiAlH$_4$ (711 mg, 18.7 mmol, 1.25 eq) in 40 mL of Et$_2$O at a rate to maintain gentle reflux. Then the mixture was stirred for another 2 h at room temperature and quenched with a saturated sodium sulfate solution. The inorganic phase was separated and extracted with diethyl ether (2 x 20 mL). The organic phase was washed with water, dried over MgSO$_4$, and evaporated. The residue was purified by flash chromatography (hexane:acetone = 5:1) to give white solid (2.88 g, 82%).

C$_{16}$H$_{26}$O (M$_r$ = 234.377). R$_f$ (hexane:acetone 3:1) = 0.44 (UV, Mostaine). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.25 (d, $J = 6.9$ Hz, 6H), 1.27 (d, $J = 6.9$ Hz, 12H), 2.88 (septet, $J = 6.9$ Hz, 2H), 3.37 (septet, $J = 6.9$ Hz, 1H), 4.77 (s, 2H), 7.26 (s, 2H).

Di-tert-butyl adipate (52)$^{7}$

At room temperature to a solution of 2,6-dimethylaniline (31.3 g, 32.7 mL, 258.3 mmol) and tBuOH (19.8 g, 25.5 mL, 266.5 mmol) in 15 mL of Et$_2$O, a solution of adipate chloride (15 g, 11.9 mL, 82 mmol) in 15 mL of ether was added dropwise using an addition funnel. The mixture was stirred for an additional 20 h at room temperature. The mixture was diluted with 300 mL of 10% (v/v) aqueous NaCl, washed with 3:1 (v/v) 2 M HCl-saturated NaCl (3 x 100 mL), 3:1 (v/v) 1 M aqueous NaOH-saturated NaCl (2 x 100 mL), saturated NaCl (1 x 100 mL) successively, dried over MgSO$_4$, distilled under HV to give the product (68-80 °C/0.014 mbar) (17.6 g, 83%).

C$_{14}$H$_{26}$O$_4$ (M$_r$ = 258.354). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.43 (s, 9H), 1.57-1.65 (m, 4H, 2CH$_2$), 2.19-2.26 (m, 4H, 2CH$_2$O).

4-(Dichloroiodo)toluene (53)$^{12}$

4-Iodotoluene (5.45 g, 25 mmol) was dissolved in glacial acetic acid (50 mL) and powdered Na$_2$S$_2$O$_8$ (8.9 g, 37 mmol, 48% excess) was added to the solution followed by the addition of conc. (36%) hydrochloric acid (20.4 mL, 244 mmol). After the mixture was warmed up to 45-50 °C, the heating was turned off and the stirring was continued for 4 h. The resulting mixture was poured into ice-water (100 g). The yellow precipitate formed was collected by filtration, washed well with ice-water until it was neutral and then with CC$_4$. The yellow crude product was air-dried in the dark (5.84 g, 80.8%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.47 (s, 3H, CH$_3$), 7.27 (d, $J = 7.7$ Hz, 2H, Ar), 8.05 (d, $J = 8.8$ Hz, 2H, Ar).

Ethyl 2-methyl-3-oxo-phenylpropanoate (54)$^{13}$
According the literatural method the product was obtained as colorless oil. Flash chromatography (hexane/TBME 15:1) gave pure product in 95% yield.

**C_{11}H_{14}O_3** \( (M_r = 206.238) \). \[ ^{1}H \text{ NMR} \ (300 \text{ MHz, CDCl}_3): \quad \delta \ 1.22 \ (t, J = 6.9 \text{ Hz, } 3 \text{H, CH}_3), \ 1.55 \ (d, J = 7.2 \text{ Hz, } 3 \text{H, CH}_3), \ 4.20 \ (q, J = 7.2 \text{ Hz, } 2 \text{H, CH}_2), \ 4.45 \ (q, J = 6.9 \text{ Hz, } 1 \text{H, CH}), \ 7.53-7.56 \ (m, 2 \text{H, Ar}), \ 7.60-7.78 \ (m, 1 \text{H, Ar}), \ 8.03-8.60 \ (m, 2 \text{H, Ar}). \]

**Benzyl 2-methyl-3-oxobutanoate (55)**

According the literatural method the product was obtained as colorless liquid. Flash chromatography (hexane/TBME 9:1) gave pure product in 90% yield.

**C_{11}H_{14}O_3** \( (M_r = 206.238) \). \[ ^{1}H \text{ NMR} \ (300 \text{ MHz, CDCl}_3): \quad \delta \ 1.31 \ (d, J = 7.2 \text{ Hz, } 3 \text{H, CH}_3), \ 3.60 \ (q, J = 7.2 \text{ Hz, } 2 \text{H, CH}_2), \ 5.21 \ (s, 2 \text{H, CH}_2\text{Ph}), \ 7.38 \ (m, 5 \text{H, Ar}). \]

**Phenyl 2-methyl-3-oxo-pentanoate (56)**

At 0 °C, to a solution of phenol (1.568 g, 16.7 mmol) and imidazole (1.36 g, 20 mmol) in 10 mL of dichloromethane, methylketene dimer (50) was added dropwise. After 30 min, CF₃COOH (1.53 mL, 2.28 g, 120 mmol) was added using a syringe. The resulting mixture was left overnight at room temperature. To the suspension TBME (100 mL) was added and the mixture was washed with NaCl (saturated), HCl (0.5 M), dried over MgSO₄ and concentrated under vacuo. The residue was purified by flash chromatography (hexane/TBME 15:1) to give the product (2.6 g, 63%).

**C_{11}H_{14}O_3** \( (M_r = 206.238) \). \[ ^{1}H \text{ NMR} \ (300 \text{ MHz, CDCl}_3): \quad \delta \ 1.54 \ (t, J = 7.2 \text{ Hz, } 3 \text{H, CH}_3), \ 1.48 \ (d, J = 1.2 \text{ Hz, } 3 \text{H, CH}_3), \ 2.69 \ (q, J = 7.2 \text{ Hz, } 2 \text{H, CH}_2), \ 3.78 \ (q, J = 7.2 \text{ Hz, } 1 \text{H, CH}), \ 7.08-7.12 \ (m, 2 \text{H, Ar}), \ 7.24-7.27 \ (m, 1 \text{H, Ar}), \ 7.36-7.41 \ (m, 2 \text{H, Ar}). \]

**4-Methoxyphenyl 2-methyl-3-oxo-pentanoate (57)**

According the literatural method starting from 2.07 g (16.7 mmol) of \( p \)-methoxyphenol and 2.24 g (20 mmol) of methylketene dimer (50) the product was obtained as colorless oil. Flash chromatography (hexane/TBME 20:1) gave pure product (3.65 g, 93%).

**C_{13}H_{16}O_4** \( (M_r = 236.264) \). \[ ^{1}H \text{ NMR} \ (300 \text{ MHz, CDCl}_3): \quad \delta \ 1.14 \ (t, J = 7.2 \text{ Hz, } 3 \text{H, CH}_3), \ 1.47 \ (d, J = 7.2 \text{ Hz, } 3 \text{H, CH}_3), \ 2.68 \ (q, J = 7.2 \text{ Hz, } 2 \text{H, CH}_2), \ 3.80 \ (q, J = 7.2 \text{ Hz, } 1 \text{H, CH}), \ 6.88 \ (d, J = 9.0 \text{ Hz, } 2 \text{H, Ar}), \ 7.00 \ (d, J = 9.2 \text{ Hz, } 2 \text{H, Ar}). \]

**Diphenylmethyl 2-methyl-3-oxo-pentanoate (58)**

According the literatural method starting from 1.3 g (11.6 mmol) of diphenylmethanol and 1.84 g (10 mmol) of methylketene dimer (50) the product was obtained as colorless oil. Flash chromatography (hexane/TBME 10:1) gave pure product in 80% yield.
3. Experimental Part

\[ C_{10}H_{20}O_3 \text{ (Mr} = 296.3603) \]. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta 1.02 \) (t, \( J = 7.2 \) Hz, 3H, CH\(_3\)), 1.39 (d, \( J = 7.2 \) Hz, 3H, CH\(_3\)), 2.50 (q, \( J = 7.2 \) Hz, 2H, CH\(_2\)), 3.63 (q, \( J = 7.2 \) Hz, 1H, CH), 6.91 (s, 1H, CH(Ph)_2), 7.33-7.34 (m, 10H, Ar).

\((2,4,6\text{-triisopropylbenzyl})\) 2-methyl-3-oxo-pentanoate (59)\(^{15}\)

According the literatural method starting from 2.56 g (10.9 mmol) of the alcohol and 1.47 g (13.1 mmol) of methylketene dimer (50) the product was obtained as colorless oil. Flash chromatography (hexane/TBME 20:1) gave pure product in 75% yield.

\[ C_{22}H_{34}O_3 \text{ (Mr} = 346.504) \]. R\(_f\) (hexane/TBME 10:1) = 0.28 (UV, Mostain). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \( \delta 1.03 \) (t, \( J = 7.2 \) Hz, 3H, MeCH\(_2\)), 1.24 (d, \( J = 6.8 \) Hz, 6H, CHMe\(_2\)), 1.26 (d, \( J = 6.8 \) Hz, 6H, CHMe\(_2\)), 1.35 (d, \( J = 7.2 \) Hz, MeCH), 2.51 (m, 2H, MeCH\(_2\)), 2.89 (sept, \( J = 6.8 \) Hz, 1H CHMe\(_2\)), 3.17 (sept, \( J = 6.8 \) Hz, 2H, 2 CHMe\(_2\)), 3.53 (q, \( J = 7.1 \) Hz, 1H, CHMe), 5.24 (d, \( J = 12.2 \) Hz, 1H, CH\(_2\)Ar), 5.32 (d, \( J = 12.2 \) Hz, 1H, CH\(_2\)Ar), 7.04 (s, 2H-Ar).

**tert-Butyl 2-oxo-cyclopentanecarboxylate (60)**\(^{16}\)

Sodium hydride (55-65% in oil), which was washed by dry hexane to remove the oil, was suspended in 80 mL of toluene. To the suspension di-tert-butyl adipate (1 g, 4 mmol) and t-butanol were added in one portion. The mixture was then refluxed with vigorous stirring for 30 min. A second portion of di-tert-butyl adipate (16 g, 62 mmol) in 40 mL of dry toluene was then added dropwise to the boiling mixture over 35 min and the mixture was boiled for another 15 h. The resulting suspension was cooled to 0 °C and sufficient 10% aqueous acetic acid was added to obtain a neutral solution. The mixture was then poured into water (150 mL) and extracted with ether (2 x 100 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (NaHCO\(_3\)) solution, dried over MgSO\(_4\), and the solvent was removed in vacuo. Distillation under reduced pressure gave the product as a colorless liquid (10.2 g, 83%).

\[ C_{10}H_{16}O_3 \text{ (Mr} = 184.23) \]. R\(_f\) (hexane:ether 2:1) = 0.25 (Mostaine). \(^1\)H NMR (250 MHz, CDCl\(_3\)): \( \delta 1.46 \) (s, 9H), 1.81-1.89 (m, 1H, CH\(_2\)), 2.08-2.15 (m, 1H, CH\(_2\)), 2.20-2.31 (m, 4H, CH\(_2\)), 3.04 (t, \( J = 8.5 \) Hz, 1H, CH).

3-Acetyl-1-phenyl-2-pyrrolidinone (61)

\(^{tBuLi\text{ (18.2 mL, 1.6 M in hexane, 29.8 mmol, 1.2 eq) was added dropwise to a solution of diisopropylamine (3.0 g, 4.2 mL, 29.8 mmol, 1.2 eq) in dry THF (10 mL) at -78 °C, under an argon atmosphere. After the solution was stirred for 20 min at 0°C, a solution of N-phenyl pyrrolidinone (4.0 g, 24.8 mmol) in dry THF (10 mL) was added dropwise at -40 °C. The reaction mixture was stirred for 30 min followed by the addition of a solution of ethyl acetate (4.73 g, 4.8 ml, 49.6 mmol) in dry THF (10 mL). The mixture was stirred for 2 h at this temperature and overnight at room temperature. The reaction mixture was quenched with saturated aqueous NH\(_4\)Cl solution.
3. Experimental Part

at 0 °C extracted with CH$_2$Cl$_2$. The combined organic layers were dried over anhydrous Na$_2$SO$_4$. Purification by column chromatography with silica gel (hexane:TBME = 1.5:1) gave the product as a yellow solid (4.07 g, 81%).

C$_{12}$H$_{13}$NO$_2$ (M$_r$ = 203.24). R$_f$ (hexane:TBME 1:1) = 0.29 (KMN$_4$). $^1$H NMR (200 MHz, CDCl$_3$): δ 2.15-2.22 (m, 1H), 2.47 (s, 3H), 2.61-2.68 (m, 1H), 3.75-3.92 (m, 1H), 7.16-7.19 (m, 1H), 7.33-7.41 (m, 2H) 7.55-7.59 (m, 2H).

$\text{Ar-[(4-Nitrophenyl)methylene]-benzenesulfonamide (62)}^{17}$

A 100-mL two-necked, round-bottomed flask is equipped with a Dean-Stark water separator and a condenser attached to an argon gas inlet and outlet connector through a mineral oil bubble. Into the flask are placed 60 mg of Amberlyst 15 ion exchange resin, 4.72 g (130 mmol) of benzenesulfonamide, 4.61 g (130.5 mmol) of benzaldehyde and 100 mL of freshly-distilled toluene. The reaction mixture is stirred and heated at reflux under an argon atmosphere. Reflux is continued until water separation ceases (approximately 18 h). The reaction mixture is cooled to room temperature and the insoluble materials are filtered. The residue in the funnel is washed with another 20 mL of toluene. The yellow solid is dissolved in 150 mL of dichloromethane and the resulting suspension is filtered and the filtrate is concentrated with a rotary evaporator to give a yellow solid and dried. The yield is 4.7 g (54%).

C$_{13}$H$_{10}$N$_2$O$_4$S (M$_r$ = 290.29). $^1$H NMR (250 MHz, CDCl$_3$): δ 7.49-7.72 (m, 3H), 8.04 (d, J = 7.2 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H), 8.33 (d, J = 8.8 Hz, 2H), 9.15 (s, 1H).

$\text{3-(4-Nitrophenyl)-2-(phenylsulfonyl)-oxaziridine (63)}^{18}$

A solution of 9.06 g (15.8 mmol) of Oxone (31.7 mmol of K$_2$N$_2$O$_2$ peroxymonosulfate) in 80 mL of water was added dropwise over 15 min to a mixture of 4 g (13.8 mmol) of sulfonimine 59 in 120 mL of toluene and 15 g (3.5 eq based on potassium peroxymonosulfate) in 80 mL of water. The reaction mixture was stirred until all sulfonimine had been consumed. The reaction was monitored by determining the ratio of sulfonimine (δ 8.7-9.2) to oxaziridine (δ 5.4-6.0) by NMR. When the reaction was complete the aqueous layer was separated and washed once with 50 mL of toluene. The combined toluene extracts were washed with 25 mL of 10% sodium sulfite and dried over anhydrous MgSO$_4$, and evaporated keeping the temperature below 40 °C to give the oxaziridine as a yellow solid.

C$_{13}$H$_{10}$N$_2$O$_4$S (M$_r$ = 306.29). $^1$H NMR (200 MHz, CDCl$_3$): δ 5.60 (s, 1H, oxaziridine), 7.60-8.29 (m, 9H, Ar).

$\text{Ethyl-2-fluoro-3-phenylpropanoate (64)}$

| CpTiCl$_3$ | 171 mg, 0.78 mmol, 5 mol% |
| Ethyl-3-phenylpropanoate | 3 g, 15.6 mmol |
| F-TEDA | 6.2 g, 17.5 mmol, 1.12 eq |
3. Experimental Part

**MeCN**

Purification (FC) 100 mL

Product hexane/TBME 8:1 oil, 2.017 g, 62.5%

C_{11}H_{11}FO_{3} (Mr = 210.20). Rf (hexane/TBME 5:1) = 0.39 (UV, Mostaine). \(^1H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.26 (t, J = 7.2 Hz, CH\(_3\)CH\(_2\)O), 2.01 (s, 3H, CH\(_3\)), 4.30 (dq, J = 7.0, 1.0 Hz, 2H, CH\(_2\)CH\(_2\)O), 5.87 (d, J = 48.9 Hz, 1H, CHF), 7.48-7.53 (m, 2H, Ph), 7.61-7.53 (m, 1H, Ph), 8.02-8.06 (m, 2H, Ph); \(^{19}F\) NMR (188.3 MHz, CDCl\(_3\)): \(\delta\) -190.27 (d, J = 48.9 Hz).

(R)-1-N,N-dimethyl[(S)-2-(bis(3,5-di(trifluoromethyl)phenyl)phosphino)ferrocenyl]ethylamine (65)

\(-\) Butyllithium (6.8 mL, 9.8 mmol, 1.1 eq, 1.6 M in pentane) was added to a solution of N,N-dimethyl[(R)-1-ferrocenylethyl]amine (2.5 g, 9.7 mmol) in 30 mL of ether at -78 °C. The resulting solution was warmed up to room temperature and stirred for 30 min, then cooled down to -78 °C, and bis[3,5-bis(trifluoromethyl)phenyl]chlorophosphine (5.27 g, 10.7 mmol) in 10 mL of ether was added via syringe. The resulting solution was stirred at -78 °C for 1 h, and stirred for 12 h at room temperature. Saturated aqueous solution of NaHCO\(_3\) was added to the solution and the product was extracted with ether. The organic phase was washed with brine, and dried over MgSO\(_4\). The solvent was removed under reduced pressure to give a crude product, which was purified by flash chromatography (hexane:EtOAc = 5:1) giving a brown oil (2.8 g, 78%).

C\(_{30}\)H\(_{24}\)F\(_{12}\)FeNP (Mr = 713.318). \(^1H\) NMR (250 MHz, CDCl\(_3\)): \(\delta\) 1.24 (d, J = 6.75 Hz, 3H, CH\(_3\)), 1.72 (s, 6H, N(CH\(_3\))\(_2\)), 3.67 (m, 1H), 4.04 (s, 5 HCp), 4.11-4.2 (m, 1H, CHMe), 4.51 (m, 1H), 7.64 (d, J = 6.5 Hz, 2 H, Ar), 7.78 (s, 1 H, Ar), 7.94 (s, 1 H, Ar), 7.98 (d, J = 6.25 Hz, 2H); \(^{31}P\) NMR (101.25 MHz, CDCl\(_3\)): \(\delta\) -19.6 (s); \(^{19}F\) NMR (188.31 MHz, CDCl\(_3\)): \(\delta\) -62.77 (s), -62.84 (s).

Bis[3,5-dimethylphenyl]chlorophosphine (66)

A Grignard mixture (prepared in situ from magnesium (4.93 g, 205.4 mmol, 2.0 eq.) and the 3,5-dimethylphenyl bromide (38 g, 27.9 mL, 215.25 mmol, 2.1 eq. ) in ether was slowly added to a solution of Et\(_2\)NPC\(_l\)\(_2\) (17.8 g, 15 mL, 102.5 mmol) in ether cooled in an ice bath. The white precipitate was filtered off under Argon. The filtrate was cooled in an ice bath and treated with a solution of HCl in ether until no Et\(_2\)NPC\(_l\)\(_2\) was detected by \(^{31}P\) NMR. The mixture was concentrated in vacuo, diluted with hexane, filtered though Celite and concentrated and distilled under HV (oil, 12 g, 42%).

\(^1H\) NMR (300.13 MHz, CDCl\(_3\)): \(\delta\) 2.30-2.38 (12H, 4CH\(_3\)), 6.99-7.51 (m, 6H, Ar); \(^{19}P\) NMR (122 MHz, CDCl\(_3\)): \(\delta\) 84.1 (s).

(S)-2-[Bis(3,5-dimethylphenyl)phosphino]-1-[(1\(R\))-1-(dimethylamino)ethyl]ferrocene (67)

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156
t-BuLi (10.2 mL, 16.4 mmol, 1.6 M in pentane) was added to a solution of N,N-dimethyl[(R)-1-ferrocenylethyl]amine (4.22 g, 16.4 mmol) in 30 mL of ether at -78 °C. The resulting solution was warmed up to room temperature and stirred for 30 min, then cooled down to -78 °C, and bis(3,5-dimethylphenyl)chlorophosphine (4.54 g, 16.4 mmol) in 10 mL of ether was added via syringe. The resulting solution was stirred at -78 °C for 1 h, and stirred for 12 h at room temperature. Saturated aqueous solution of NaHCO₃ was added to the solution and the product was extracted with ether. The organic phase was washed with brine, and dried over MgSO₄. The solvent was removed under reduced pressure to give a crude product, which was purified by flash chromatography (hexane:EtOAc = 5:1 to 2:1) to give a brown oil (3.55 g, 44%).

C₃₀H₃₆FeNP (Mₑ = 497.432). ¹H NMR (300 MHz, CDCl₃): δ 1.39 (d, J = 6.9 Hz, 3H, CH₃), 1.94 (s, 6H, NMe₂), 2.29 (s, 6H, Me-Ar), 2.42 (s, 6H, MeAr), 3.40 (m, 1H), 4.04 (s, 5H, Cp), 4.22-4.26 (m, 1H, CHCH₃), 4.32-4.33 (m, 1H), 4.46 (m, 1H), 6.88, 6.91, 6.94, 7.08, 7.37 and 7.39 (s, Ar); ³¹P NMR (101.25 MHz, CDCl₃): δ -22.2 (s).

Bis{(R)-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyl}cyclohexylphosphine
(R)-(S)-Pigiphos (68)

(R)-(S)-PPFA (5.7 g, 12.95 mmol) was dissolved at 40 °C in degassed CH₃COOH (30 mL), containing TFA (0.977 mL, 12.95 mmol). H₂PCy (0.86 mL, 6.475 mmol) was added and the mixture was stirred at 80 °C for 4 h. The solvent was removed under reduced pressure (HV, 60 °C) and ethyl acetate was added. The resulting precipitate was filtered and washed with hexane:ethyl acetate = 1:1, yielding the pure product as orange solid (4.5 g, 77%).

C₅₄H₅₅Fe₂P₃ (Mₑ = 908.6258). ¹H NMR (250 MHz, CD₂Cl₂): δ 0.71-1.61 (m, 11H, Cy), 1.66 (d, J = 7.75 Hz, 3H, CH₃), 1.68 (d, J = 7.75 Hz, 3H, CH₃), 2.92-2.95 (m, 1H, CHCH₃), 3.19-3.22 (m, 1H, CHCH₃), 3.84 (s, 5H, Cp’), 3.88 (s, 5H, Cp’), 3.93 (s, 1H, CHCp), 4.04 (s, 2H, Cp), 4.12 (s, 1H, Cp), 4.29 (d, J = 7.0 Hz, 2H, Cp), 7.13-7.23 (m, 10 H, Ph), 7.43 (m, 6H, Ph), 7.68 (m, 4H, Ph); ³¹P NMR (101.25 MHz, CD₂Cl₂): δ -25.66 (d, J = 29.16 Hz, P-Ph), -25.74 (d, J = 12.0 Hz, P-Ph), 17.47 (dd, J = 29.8, 11.2 Hz, P-Cy); Anal. Calcd for C₅₄H₅₅Fe₂P₃: C, 71.38; H, 6.10. Found: C, 71.27; H, 6.18.

Bis{(1R)-1-(S)-2-[bis-[3,5-bis(trifluoromethyl)phenyl]phosphino]ferrocenylethyl}cyclohexylphosphine
(R)-(S)-(3,5-(CF₃)₂Ph)-Pigiphos (69)

(R)-(S)-PPFA-3,5-CF₃Ph (1.58 g, 2.22 mmol) was dissolved at 40 °C in degassed CH₃COOH (30 mL). H₂PCy (146.9 µL, 1.11 mmol) was added and the mixture was stirred at 80 °C for 10 h. The solvent was removed under reduced pressure (HV, 60 °C).
3. Experimental Part

The residue was purified by flash chromatography (hexane:TBME = 100:1), yielding the pure product as orange crystals (1.21 g, 75%).

\( \text{C}_{62}\text{H}_{47}\text{F}_{24}\text{Fe}_{2}\text{P}_{3} \) (\( M_r = 1452.6095 \)). \( ^{1}H \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 0.70-1.70 (m, 17H, Cy and 2CH\(_3\)), 2.77-2.79 (m, 1H, CHCH\(_3\)), 3.07-3.10 (m, 1H, CHCH\(_3\)), 3.83 (s, 5H, Cp), 3.86 (s, 5H, Cp'), 3.92 (br, 1H), 3.98 (br, 1H), 3.99 (br, 1H), 4.28 (br, 1H), 4.37 (m, 1H), 4.49 (m, 1H), 7.64-8.05 (m, 12H, Ar), \( ^{31}P \) NMR (81 MHz, CDCl\(_3\)): \( \delta \) 19.6 (dd, \( J = 35.1, 12.7 \) Hz, PCy), -22.5 (d, \( J = 13.3 \) Hz, PAr\(_2\)), -23.3 (d, \( J = 35.1 \) Hz, PAr\(_2\)), \( ^{19}F \) NMR (188.31 MHz, CDCl\(_3\)): \( \delta \) -62.7 (s), -62.8 (s), -62.8 (s), -62.8 (s), -63.0 (s); Anal. Calcd for \( \text{C}_{62}\text{H}_{47}\text{F}_{24}\text{Fe}_{2}\text{P}_{3} \): C, 51.26; H, 3.26. Found: C, 51.34; H, 3.39.

Bis\((1^R)-1-(\text{S})-2-[\text{bis-(3,5-dimethylphenyl)phosphino}]\text{ferrocenylethyl}\)cyclohexylphosphine

\((R)-(S)-(3,5-(\text{CH}_3)\text{Ar})\)-Pigiphos (70)

\((R)-(S)-\text{PPFA-3,5-CH}_3\text{Ar} \) (2.45 g, 4.9 mmol) was dissolved at 40 °C in degassed CH\(_3\)COOH (20 mL). \( \text{H}_2\text{PCy} \) (326 uL, 264 mmol) was added and the mixture was stirred at 80 °C for 10 h. The solvent was removed under reduced pressure (HV, 60 °C) and the residue was purified by flash chromatography (hexane:TBME = 10:1) to give product (1.154 g, 49%).

\( \text{C}_{60}\text{H}_{41}\text{FeP}_{3} \) (\( M_r = 1020.838 \)). \( ^{1}H \) NMR (250 MHz, CDCl\(_3\)): \( \delta \) 0.70-1.70 (m, 17H, Cy and 2CH\(_3\)), 2.29 (s, 6H, 2CH\(_3\)-Ar), 2.33 (s, 6H, 2CH\(_3\)-Ar), 2.41 (s, 12H, 4CH\(_3\)-Ar), 2.85 (b, 1H, CHCH\(_3\)), 3.22 (b, 1H, CHCH\(_3\)), 3.83 (s, 5H, Cp), 3.96 (s, 5H, Cp), 3.96 (s, 1H, C\(_5\)H\(_3\)), 4.04 (s, 1H, C\(_5\)H\(_3\)), 4.09 (s, 1H, C\(_5\)H\(_3\)), 4.13 (s, 1H, C\(_5\)H\(_3\)), 4.26 (s, 1H, C\(_5\)H\(_3\)), 4.34 (s, 1H, C\(_5\)H\(_3\)), 6.97-7.07 (m, 8H, Ar), 7.32 (d, \( J = 8.25 \) Hz, 2H, Ar), 7.39 (d, \( J = 8.25 \) Hz, 2H, Ar); \( ^{31}P \) NMR (101 MHz, CDCl\(_3\)): \( \delta \) 15.3 (dd, \( J = 26.8, 6.87 \) Hz, PCy), -25.2 (d, \( J = 27 \) Hz, PAr\(_2\)), -25.3 (d, \( J = 5.3 \) Hz, PAr\(_2\)).

Bis\((1^R)-1-(\text{S})-2-[\text{bis-(2-trifluoromethylphenyl)phosphino}]\text{ferrocenylethyl}\)cyclohexylphosphine

\((R)-(S)-(2-CF\(_3\)-Ph)\)-Pigiphos (71)

\((R)-(S)-\text{PPFA-2-CF}_3\text{Ph} \) (500 mg, 0.866 mmol) was dissolved at 40 °C in degassed CH\(_3\)COOH (20 mL). \( \text{H}_2\text{PCy} \) (57.4 uL, 0.433 mmol) was added and the mixture was stirred at 80 °C for 10 h. The solvent was removed under reduced pressure (HV, 60 °C) and ethyl acetate was added. The resulting precipitate was filtered and washed with hexane:ethyl acetate = 5:1, yielding the pure product as orange crystals (252 mg, 49%).

\( \text{C}_{58}\text{H}_{51}\text{F}_{12}\text{FeP}_{3} \) (\( M_r = 1180.6177 \)). \( ^{1}H \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 0.53-1.40 (m, 11H, Cy), 1.49-1.53 (m, 3H, CH\(_3\)), 1.61-1.66 (m, 3H, CH\(_3\)), 2.83-2.87 (m, 1H, CHCH\(_3\)), 3.90-3.11 (m, 1H, CHCH\(_3\)), 3.80 (s, 5H, Cp), 3.83 (s, 5H, Cp'), 3.94 (br, 1H), 4.00 (br, 1H), 4.07 (br, 1H), 4.12 (br, 1H), 4.26-4.29 (m, 2H), 7.23-7.88
3. Experimental Part

(m, 16H, Ar); $^{31}$P NMR (121.5 MHz, CDCl$_3$): $\delta$ 18.51 (dd, $J$ = 53.6, 18.6 Hz, PCy), -34.26 to -37.47 (m, PAr); $^{19}$F NMR (188.31 MHz, CDCl$_3$): $\delta$ -54.8 (dq, $J$ = 22.6, 5.4 Hz), -55.1 (dq, $J$ = 20.3, 5.0 Hz), -58.1 (pentet, $J$ = 5.5 Hz), 58.3 (pentet, $J$ = 5.3 Hz); Anal. Calcd for C$_{38}$H$_{31}$F$_2$Fe$_2$P$_3$: C, 59.01; H, 4.35. Found: C, 58.76; H, 4.60.

4-Cyano-2,2,6,6-tetramethyl-3,5-heptanedione (72)$^{19}$

To a 100 mL Schlenk, 30 mL of dichloromethane and 9.2 g (10.54 mL, 0.05 mol) of 2,2,6,6-tetramethyl-3,5-heptanedione were added, followed by the addition of 3.5 g (2.18 mL, 0.025 mol) of CISO$_2$NCO dropwise over a period of 5 min. The colorless solution was stirred for another 5 min, giving a white precipitate. Subsequently, 3.65 g (3.87 mL, 0.05 mol) of DMF was added. After 30 min, the organic solution was washed until it was neutral, dried over Na$_2$SO$_4$, and the solvent was removed in vacuo. Purification through crystallization (pentane-diethyl ether) gave the product as needle crystal (3 g, 29%).

C$_{12}$H$_{19}$N$_{2}$O$_2$ (Mr = 209.2848). Rf (hexane/TBME 100:1) = 0.17 (UV). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.40 (s, 18 H, CH$_3$), 18.77 (s, OH); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 26.9 (CH$_3$), 42.3 (C), 84.4 (C), 119.0 (CN), 208.9 (CO).

2-Methyl-1,3-diphenyl-1,3-propanedione (73)$^{20}$

Propiophenone (2.0 g, 1.5 mL, 15 mmol) was added dropwise to a solution of LiHMDS (15 mL, 1.0 M in THF, 15 mmol) in 100 mL of THF over 15 min at room temperature. The resulting solution was stirred for further 15 min prior to the addition of a solution of benzoyl fluoride (1.86 g, 1.63 mL, 15 mmol) in 20 mL of THF. The reaction mixture was stirred for 15 min and subsequently extracted with ethyl acetate (3 x 50 mL). The combined organic solvents were dried over magnesium sulfate and concentrated in vacuo. Purification was achieved by flash chromatography (hexane:ethyl acetate = 10:1) to give the product as colorless oil (2.12 g, 59%).

C$_{16}$H$_{14}$O$_2$ (Mr = 238.281). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.61 (d, $J$ = 6.9 Hz, 3H, CH$_3$), 5.27 (q, $J$ = 6.9 Hz, 1H, CH), 7.43 (m, 4H, Ar), 7.54-7.60 (m, 2H, Ar), 7.95-7.97 (m, 4H, Ar).

2-Methyl-1-(2,4-dimethoxyphenyl)-1,3-butanedione (74)

To a solution 2,4-dimethoxyphenyl-1,3-butanedione (2 g, 9.0 mmol) in 50 mL of THF was added KN(SiMe$_3$)$_2$ (1.795 g, 9.0 mmol) at room temperature. A white suspension was obtained followed by the MeQ addition of iodomethane (1.43 g, 0.629 mL, 1.1 eq) via syringe. The mixture was stirred overnight and water (10 mL) was added. The organic phase was washed with brine, dried over MgSO$_4$, concentrated and purified by chromatography (hexane:ethyl acetate = 2:1) to give yellowish oil (1.81 g, 85%) as product.

C$_{13}$H$_{16}$O$_4$ (Mr = 236.264). $^1$H NMR (250 MHz, CDCl$_3$): $\delta$ 1.36 (d, $J$ = 7 Hz, 3H, CH$_3$), 2.20 (s, 3H, CH$_3$O), 3.89 (s, 6H, 2CH$_3$O), 4.42 (q, $J$ = 7 Hz, 1H, CH), 6.47 (d, $J$ = 2 Hz, 1H, Ar), 6.58 (d, $J$ = 8.75 Hz, 1H, Ar), 7.88 (d, $J$ = 8.75 Hz, 1H, Ar). $^{13}$C NMR (75.5 MHz): $\delta$ 13.2,
3. Experimental Part

28.4, 55.2, 55.6, 98.3, 104.7, 105.7, 130.3, 160.3, 165.0, 197.1, 205.8; Calcd for C$_{13}$H$_{16}$O$_4$: C, 66.09; H, 6.83. Found: C, 66.00; H, 6.80.

3.4 References

### Crystallographic Data

Crystal data and structure refinement for 17

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Appendix

Crystal data and structure refinement for PIO (the less polar isomer, obtained via ATH of racemic fluorinated lactam using S,S-Ru)

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\[b = 5.5446(5) \text{ Å}, \beta = 96.427(2) \text{ deg.}\]
\[c = 11.5709(10) \text{ Å}, \gamma = 90 \text{ deg.}\]
Volume  538.84(8) Å³
Z, Calculated density  2, 1.376 Mg/m³
Absorption coefficient  0.105 mm⁻¹
F(000)  236
Crystal size  0.40 x 0.08 x 0.06 mm
Data collection  Siemens SMART PLATFORM with CCD Detector
Graphite monochromator
Detector distance  50 mm
Method; exposure time/frame  Ω-scans; \(t = \text{sec}\)
Solution by  direct methods
Refinement method  full matrix least-squares on F², SHELXTL
Theta range for data collection  1.77 to 28.19 deg.
Limiting indices  -6<=h<=11, -7<=k<=7, -14<=l<=13
Reflections collected / unique  3441 / 2340 \([R(\text{int}) = 0.0606]\)
Completeness to 0 = 28.19  93.7 %
Max. and min. transmission  0.9937 and 0.9592
Refinement method  Full-matrix least-squares on F²
Data / restraints / parameters  2340 / 1 / 145
Goodness-of-fit on F²  1.046
Final R indices [I>2σ(I)]  R₁ = 0.0386, wR₂ = 0.0965
R indices (all data)  R₁ = 0.0484, wR₂ = 0.1022
Absolute structure parameter  0.8(9)
Largest diff. peak and hole  0.200 and -0.161 e Å⁻³
Crystal data and structure refinement for **P3** (obtained via fluorination using **R,R-Ti** followed by ATH using **S,S-Ru**)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{12}H_{15}F_{3}O_{3}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>226.24</td>
</tr>
<tr>
<td>Temperature</td>
<td>200(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>?</td>
</tr>
</tbody>
</table>
| Unit cell dimensions                           | \( a = 8.3541(11) \) Å \( \alpha = 90° \)  
   \( b = 5.1974(7) \) Å \( \beta = 100.943(3)° \)  
   \( c = 13.7832(18) \) Å \( \gamma = 90° \)          |
| Volume                                         | 587.58(13) Å³                        |
| Z, Calculated density                          | 2, 1.279 Mg/m³                       |
| Absorption coefficient                         | 0.101 mm⁻¹                           |
| F(000)                                         | 240                                  |
| Crystal size                                   | 1.00 x 0.18 x 0.16 mm                |
| Data collection                                | Siemens SMART PLATFORM with CCD Detector |
| Solution by                                     | direct methods                       |
| Refinement method                              | full matrix least-squares on F², SHELXTL |
|  \( \theta \) range for data collection        | 1.50 to 28.35 deg.                   |
| Limiting indices                               | \(-11 \leq h \leq 11, -5 \leq k \leq 6, -18 \leq l \leq 8\) |
| Reflections collected / unique                 | 3512 / 2492 [R(int) = 0.0158]        |
| Completeness to \( \theta = 28.35 \)           | 99.9 %                               |
| Absorption correction                          | Empirical                            |
| Max. and min. transmission                     | 0.9840 and 0.9059                    |
| Refinement method                              | Full-matrix least-squares on F²      |
| Data / restraints / parameters                  | 2492 / 1 / 148                      |
| Goodness-of-fit on F²                           | 1.080                                |
| Final R indices [I>2σ(I)]                      | R1 = 0.0401, wR2 = 0.0992            |
| R indices (all data)                           | R1 = 0.0412, wR2 = 0.1002            |
| Absolute structure parameter                   | -0.4(8)                              |
| Largest diff. peak and hole                     | 0.225 and -0.218 e.A⁻³              |
Appendix

Crystal data and structure refinement for NiA \([\text{Ni(Pigiphos)(CH}_3\text{CN})(\text{BF}_4)_2 \text{CH}_2\text{Cl}_2]\)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>(\text{C}<em>{57}\text{H}</em>{55}\text{B}<em>2\text{C}</em>{12}\text{F}_8\text{Fe}_2\text{NNiP}_3)</td>
</tr>
<tr>
<td>Formula weight</td>
<td>1261.86</td>
</tr>
<tr>
<td>Temperature</td>
<td>546(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Orthorhombic, P212121</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 14.0065(15)) Å, (a = 90^\circ) (b = 19.892(2)) Å, (\beta = 90^\circ) (c = 20.287(2)) Å, (\gamma = 90^\circ)</td>
</tr>
<tr>
<td>Volume</td>
<td>5652.2(10) Å³</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4, 1.483 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>1.081 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>2580</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.64 x 0.53 x 0.33 mm</td>
</tr>
<tr>
<td>Data collection</td>
<td>Siemens SMART PLATFORM with CCD Detector</td>
</tr>
<tr>
<td>Graphite monochromator</td>
<td></td>
</tr>
<tr>
<td>Detector distance</td>
<td>30 mm</td>
</tr>
<tr>
<td>Method, exposure time/frame</td>
<td>(\Omega)-scans; (t = \text{sec})</td>
</tr>
<tr>
<td>Solution by</td>
<td>direct methods</td>
</tr>
<tr>
<td>Refinement method</td>
<td>full matrix least-squares on (F^2), SHELXTL</td>
</tr>
<tr>
<td>(\theta) range for data collection</td>
<td>1.43 to 26.37 deg.</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>(-17 \leq h \leq 17, -24 \leq k \leq 24, -25 \leq l \leq 25)</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>51434 / 11572 [R(int) = 0.0772]</td>
</tr>
<tr>
<td>Completeness to (\theta = 26.37)</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Empirical</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.7169 and 0.5447</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on (F^2)</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>11572 / 4 / 713</td>
</tr>
<tr>
<td>Goodness-of-fit on (F^2)</td>
<td>1.020</td>
</tr>
<tr>
<td>Final R indices [I&gt;2(\sigma(I))]</td>
<td>(R1 = 0.0375, wR2 = 0.0994)</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>(R1 = 0.0406, wR2 = 0.1016)</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>-0.001(9)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.649 and -0.398 e.A³</td>
</tr>
</tbody>
</table>
Crystal data and structure refinement for $\text{Ni}_8$

$[\text{Ni}(\text{Pigiphos})(\text{CH}_2=\text{CCH}_3\text{CN})](\text{BF}_4)_2\cdot \text{CH}_2\text{Cl}_2$

Empirical formula: $\text{C}_{59}\text{H}_{62}\text{B}_2\text{Cl}_2\text{F}_8\text{Fe}_2\text{NNiP}_3$

Formula weight: 1292.94

Temperature: 195(2) K

Wavelength: 0.71073 Å

Crystal system, space group: Orthorhombic, $P2_12_12_1$

Unit cell dimensions:
- $a = 14.0239(7)$ Å $\alpha = 90^\circ$
- $b = 19.8015(9)$ Å $\beta = 90^\circ$
- $c = 20.4101(10)$ Å $\gamma = 90^\circ$

Volume: 5667.8(5) Å$^3$

Z, Calculated density: 4, 1.515 Mg/m$^3$

Absorption coefficient: 1.080 mm$^{-1}$

$F(000)$: 2656

Crystal size: 0.65 x 0.34 x 0.17 mm

Detector distance: 50 mm

Method; exposure time/frame: $\Omega$-scans; $t = 20$ sec

Solution by: direct methods

Theta range for data collection: 1.43 to 28.34 deg.

Limiting indices: $-18 <= h <= 18$, $-26 <= k <= 26$, $-27 <= l <= 27$

Reflections collected / unique: 59125 / 14125 $[R(\text{int}) = 0.0306]$

Completeness to $\theta = 28.34$: 99.9%

Absorption correction: Empirical

Max. and min. transmission: 0.8377 and 0.5404

Refinement method: Full-matrix least-squares on $F^2$

Data / restraints / parameters: 14125 / 0 / 706

Goodness-of-fit on $F^2$: 1.160

Final $R$ indices [$I>2\sigma (I)$]: $R1 = 0.0510$, $wR2 = 0.1271$

$R$ indices (all data): $R1 = 0.0527$, $wR2 = 0.1283$

Absolute structure parameter: 0.030(11)

Largest diff. peak and hole: 0.792 and -0.605 eÅ$^{-3}$
Appendix

Crystal data and structure refinement for **P28**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical formula</strong></td>
<td>C_{10}H_{13}NO_{2}</td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
<td>179.22</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>294(2) K</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>0.71073 Å</td>
</tr>
<tr>
<td><strong>Crystal system, space group</strong></td>
<td>Triclinic, P1</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>a</strong></td>
<td>6.5415(5) Å</td>
</tr>
<tr>
<td><strong>α</strong></td>
<td>65.0120(10)°</td>
</tr>
<tr>
<td><strong>b</strong></td>
<td>12.5538(9) Å</td>
</tr>
<tr>
<td><strong>β</strong></td>
<td>87.8170(10)°</td>
</tr>
<tr>
<td><strong>c</strong></td>
<td>13.6934(9) Å</td>
</tr>
<tr>
<td><strong>γ</strong></td>
<td>86.1890(10)°</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>1016.94(13) Å</td>
</tr>
<tr>
<td><strong>Z, Calculated density</strong></td>
<td>1, 1.171 Mg/m³</td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
<td>0.082 mm⁻¹</td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
<td>384</td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
<td>0.80 x 0.50 x 0.20 mm</td>
</tr>
<tr>
<td><strong>Data collection</strong></td>
<td>Siemens SMART PLATFORM with CCD Detector</td>
</tr>
<tr>
<td><strong>Graphite monochromator</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Detector distance</strong></td>
<td>50 mm</td>
</tr>
<tr>
<td><strong>Method, exposure time/frame</strong></td>
<td>Ω-scans; t = 8 sec</td>
</tr>
<tr>
<td><strong>Solution by</strong></td>
<td>direct methods</td>
</tr>
<tr>
<td><strong>Refinement method</strong></td>
<td>full matrix least-squares on F², SHELXTL</td>
</tr>
<tr>
<td><strong>θ range for data collection</strong></td>
<td>1.64 to 20.81 deg.</td>
</tr>
<tr>
<td><strong>Limiting indices</strong></td>
<td>-6≤h≤6, -12≤k≤12, -13≤l≤13</td>
</tr>
<tr>
<td><strong>Reflections collected / unique</strong></td>
<td>5511 / 4213 [R(int) = 0.0851]</td>
</tr>
<tr>
<td><strong>Completeness to θ = 20.81</strong></td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>Absorption correction</strong></td>
<td>Empirical</td>
</tr>
<tr>
<td><strong>Max. and min. transmission</strong></td>
<td>0.9838 and 0.9375</td>
</tr>
<tr>
<td><strong>Refinement method</strong></td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td><strong>Data / restraints / parameters</strong></td>
<td>4213 / 3 / 469</td>
</tr>
<tr>
<td><strong>Goodness-of-fit on F²</strong></td>
<td>1.033</td>
</tr>
<tr>
<td><strong>Final R indices [I&gt;2σ(I)]</strong></td>
<td>R1 = 0.0761, wR2 = 0.2016</td>
</tr>
<tr>
<td><strong>R indices (all data)</strong></td>
<td>R1 = 0.0774, wR2 = 0.2043</td>
</tr>
<tr>
<td><strong>Absolute structure parameter</strong></td>
<td>-0.7(16)</td>
</tr>
<tr>
<td><strong>Largest diff. peak and hole</strong></td>
<td>0.342 and -0.255 eÅ⁻³</td>
</tr>
</tbody>
</table>
Appendix

Curriculum Vitae

1970, 24th, Dec. Born in Xuzhou, P. R. China

1989 – 1993: B. Sc., Chemistry
Department of Chemistry, Suzhou University, P. R. China

1993 – 1995 Teacher in No.2 High School
Peixian County Jiangsu Province P.R. China.

1995 – 1998: M.Sc. in the Group of Prof. Z. Cao
in Organic Chemistry, Department of Chemistry, Suzhou University,
P. R. China

1998 – 2001 Research Associate in the Group of Prof. X. Lu and Prof. Z. Zhang,
State Key Laboratory Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences, China

2003 – 2006: Ph. D in the Group of Prof. Dr. A. Togni
Department of Chemistry and Applied Biosciences,
Swiss Federal Institute of Technology (ETH Zurich), Switzerland